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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

NOVEMBER 1938

THE CHEMISTRY AND BIOLOGY OF MALE SEX HORMONES*

F. C. KOCH

Professor of Biochemistry, The University of Chicago

INTRODUCTION

WHAT is now interpreted as the general physiological response to a lack of male sex hormone in the male is no doubt the earliest observation in endocrinology in man and in domestic animals. Castration was practised among the ancients, probably earliest in China. In the Bible we find reference to eunuchs "so born from their mother's womb," eunuchs made by man, and "eunuchs which made themselves eunuchs for the Kingdom of Heaven's sake." While the motives for castration in men were in the main to prevent reproduction, the profound general physiological changes must have been observed in man and were intentionally produced in domestic animals. It is not surprising that these rather accidental observations early led to attempts to replace the missing organs by homo-transplantation. The first testis transplantation on record appears to be by John Hunter in hens in 1762,[1] but the first true replacement studies by transplantation were conducted by the German physician, Berthold in 1849, in the capon.[2] He concluded that the regeneration of

* Lecture delivered April 21, 1938.

Fig. 1

the capon's comb by the testis transplant must be due to "the influence of it upon the blood, and then to the influence of the blood on the organism as a whole, with the nervous system no doubt playing a very important rôle." In spite of these early physiological studies on the testis many less obvious endocrine organs have yielded their secrets to our combined biological and chemical attack much more readily than the testis. The reasons for slow progress in the case of the testicle are now clear because we know that testis tissue, contrary to most other endocrine organs and contrary to most earlier claims, contains its hormone in such low concentrations that considerable fractionation and concentration must be accomplished before it can be detected by biological or chemical methods.

The Isolation of Pure Androgens and Their Structural Formulae

The first investigator to contribute materially to this phase of the problem was McGee[3,4] who also first introduced the use of the brown leghorn capon for assay purposes. Following his discovery, detailed quantitative studies on the comb-growth reaction in the capon led to the development of several very satisfactory quantitative assay methods for androgens. These methods have been used to great advantage in studying

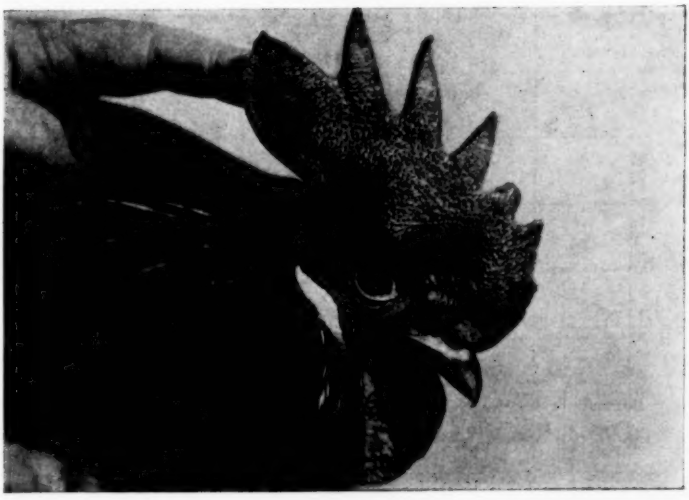


Fig. 2

the distribution of androgens, in the fractionation of extracts, and in the separation of pure androgens. A qualitative result from the intensive treatment over a period of eighteen days is shown in Figs. 1 and 2 and the quantitative relation between dosage and comb-growth response by the curve in Fig. 3.[5] With these methods developed it was soon found that men's urine is a good source for androgenic activity and it was also found that testis-tissue concentrates which had been standardized by the capon method could be used to regenerate the atrophied accessory sex organs of castrated rats and guinea pigs.

From this time on rapid strides were made in the chemistry of androgens. Butenandt[6] was the first to separate androsterone (III, page 659) in pure crystalline form from human urine-concentrates. In 1934 he and Tscherning[7] assigned the correct formula thereto (III) and also showed its relation to dehydroandrosterone (II), another androgen from human urine. The suggested relation of these compounds to cholesterol (I) is obvious, but the proof of this relationship involved a number of possible isomerisms, a problem which was beautifully solved by the classical work of Ruzicka and his associates.[8] These investigators assumed that if androsterone (III) could be formed from cholesterol (I), it

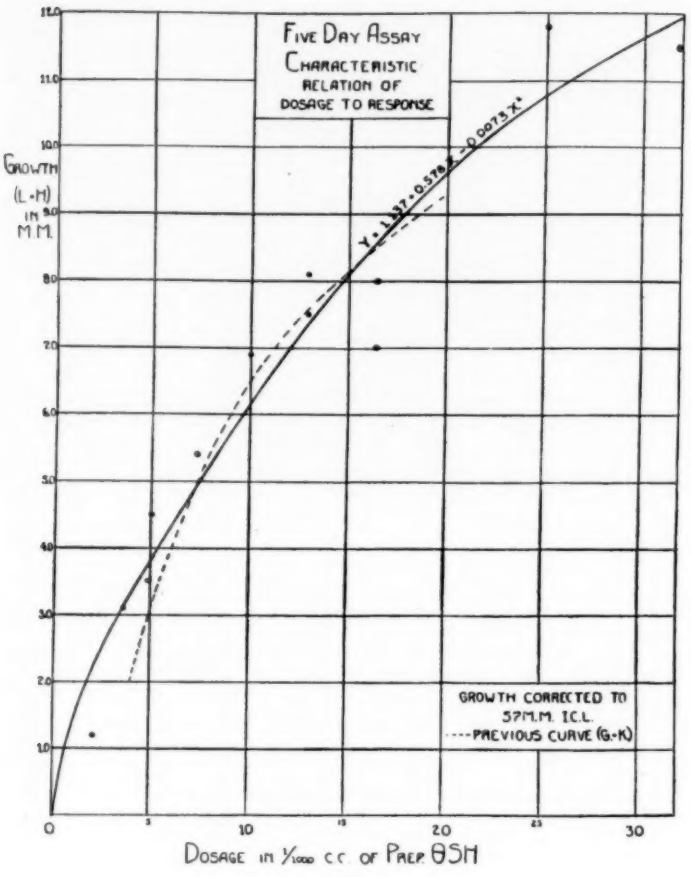
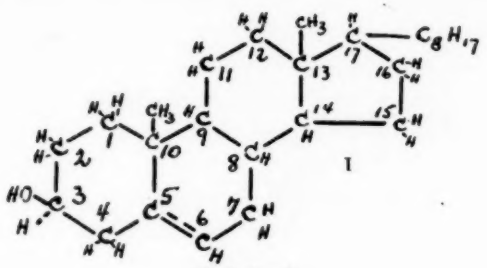


Fig. 3

might have the structure of one of the four possible isomers (IV, V, VI, and VII). The four isomers were prepared and V was found to be identical chemically and in biological activity with the Butenandt product obtained from urine. The important steps in the synthetic degradation of cholesterol to androsterone are given on page 661.

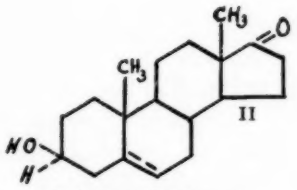
When androsterone was first separated, it appears to have been quite generally assumed that male-hormone activity probably would be limited to it and to dehydroandrosterone. In other words, it was thought that

STRUCTURAL RELATIONS BETWEEN CHOLESTEROL AND ANDROGENS



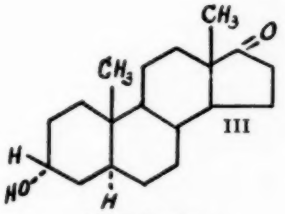
I

Cholesterol



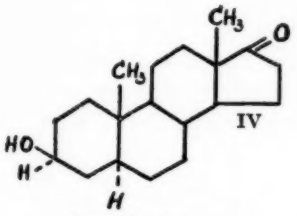
II

Dehydroandrosterone
(250—300 γ)



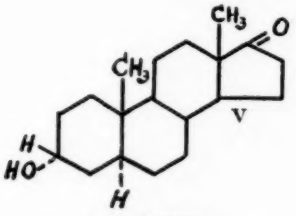
III

Androsterone
(100 γ)



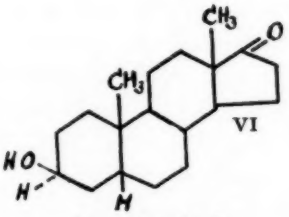
IV

Iso-androsterone
from dihydrocholesterol
(700—770 γ)



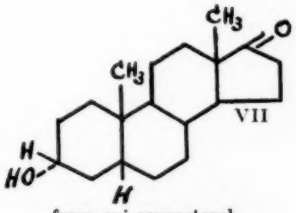
V

Androsterone
from epi-dihydrocholesterol
(100 γ)



VI

from coprosterol
(1000 γ = 0 activity)



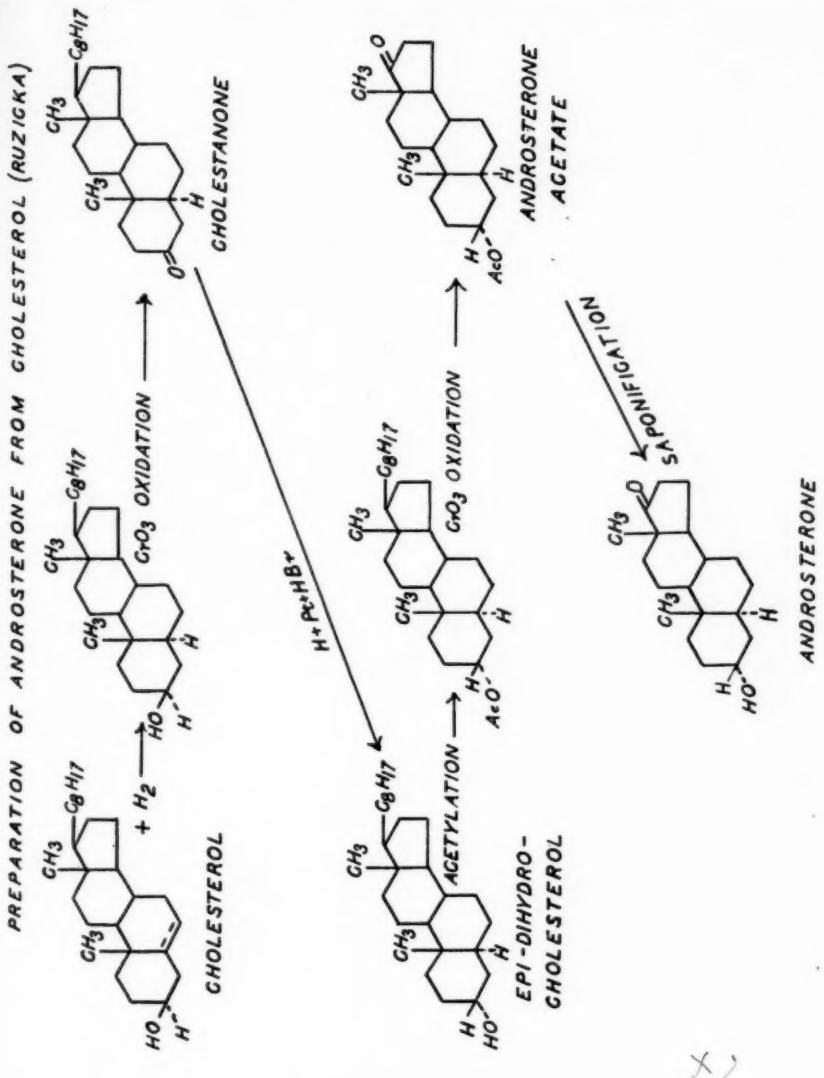
VII

from epi-coprosterol
(1000 γ = 0 activity)

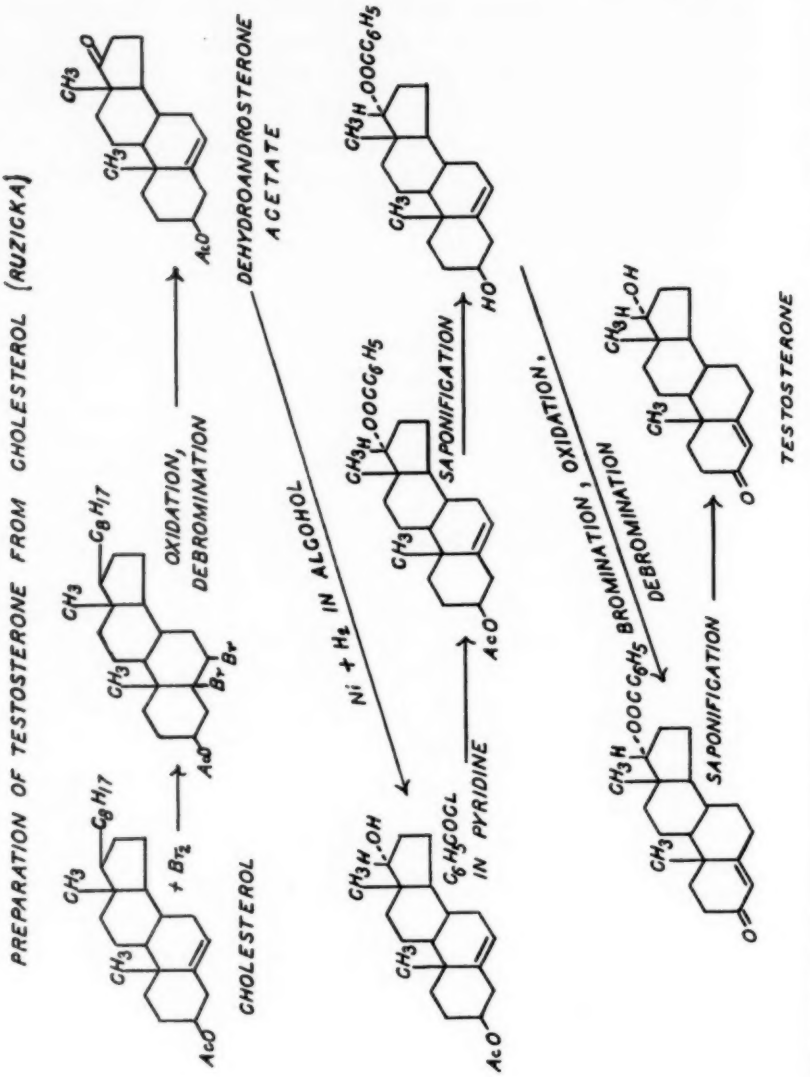
The γ values represent the equivalent of the international capon unit or 100 γ of androsterone.

it probably represented the true secretion from the testicles. However, Gallagher and I[9] had already obtained concentrates from bull testis-tissue which were five to ten times as potent per unit weight as crystalline androsterone and we had also demonstrated a difference in the action of alcoholic potassium hydroxide on testis-tissue and urinary concentrates of androgens.[10] The former was destroyed, but the latter was not. Furthermore, Laqueur and his group[11] had shown by comparative assays on capons and castrated rats that the ratio expressed as rat units over capon units for various fractions and concentrates showed tremendous fluctuations. Stimulated by these findings, David, *et al.*[12] finally succeeded in separating the third androgen, testosterone, from bull testis-tissue. He did not determine its structure but within a very short time after he had announced his discovery, the Butenandt[13] and Ruzicka[14] groups independently reported the preparation of the identical substance by the synthetic degradation of cholesterol. The fact that the androgenic activity in testis-tissue concentrates had been found to be alkali-labile stimulated the organic chemist to attempt to produce from cholesterol a variety of derivatives which one would expect to be alkali-labile. The probable structure of such a group was indicated by the observation that progesterone (XVIII, p. 666) was known to be alkali-labile. Hence the attempts to prepare Δ^4-androstenone-3 derivatives of various kinds. Of these, Δ^4-androstenolone-17,3 proved to be identical with testosterone (VIII). The steps involved in the synthetic degradation of cholesterol to testosterone are given on page 662.

With the advancement of our knowledge of the chemistry of sterols and bile acids, which was gained mainly through the interest aroused in these substances as a result of vitamin D and sex hormone studies, the organic chemists soon produced innumerable compounds more or less related to the natural androgens. Naturally the isolation of other androgens from natural sources also became less difficult. To date over fifty such androgenic substances are known. On pages 663 and 664 a few of the more typical androgens are given; they are grouped as saturated and unsaturated compounds. The potencies are expressed in micrograms equivalent to the international unit of 100 micrograms of androsterone as assayed on the capon and in most cases also the activity as determined in the rat. A study of these pages shows that stereoisomerism is a very important factor in determining the activity of these compounds and that the relative potencies of these substances on capons and rats vary



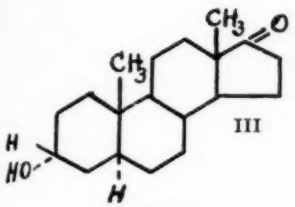
considerably. Thus, in the saturated series, the active forms are those compounds which have the hydrogen on carbon 5 in a *trans* position with reference to the CH_3 group on carbon 10. Expressed in other words this means that the saturated compounds which have been derived from dihydrocholesterol or epidihydrocholesterol are likely to be more active



than the isomers obtained from coprosterol or epicoprosterol. This is an excellent illustration of the delicate and detailed architecture of some of our physiological mechanisms.

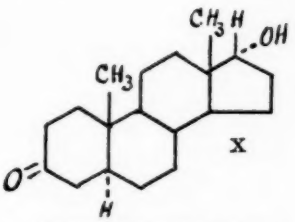
The configuration of the secondary alcohol groups in positions 3 and

SOME SATURATED ANDROGENS



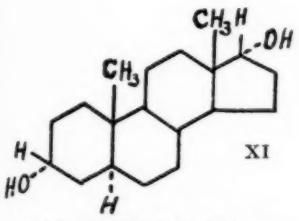
III

Androsterone
(from men's urine)
(100 γ)*
(500 γ/10/68 mg.)†



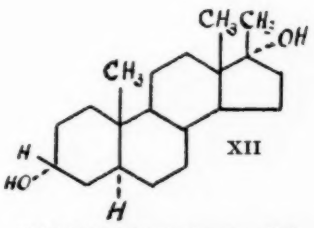
X

Androstanolone-17 trans, 3
(not found in nature)
(25—30 γ)
(rat test?)



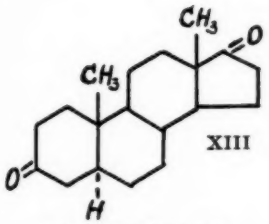
XI

Androstanediol-3 cis, 17 trans
(not found in nature)
(20—35 γ)
(100 γ/10/43 mg.)



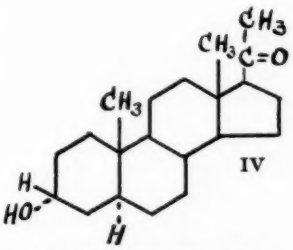
XII

17-Methyl (cis)-Androstanediol-3 cis, 17
(not found in nature)
(25—40 γ)
(200 γ/10/35 mg.)



XIII

Androstanedione-3,17
(not found in nature)
(120—125 γ)
(200 γ/10/29 mg.)

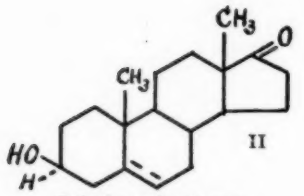


IV

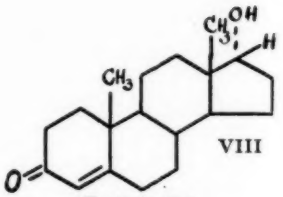
Epi-*allo*-pregnanolone-3,20
(from women's pregnancy urine)
(androgenic in capons and rats)

* equivalent of international unit on capon.
† per day for 10 days in rat with weight of seminal vesicle in milligrams.

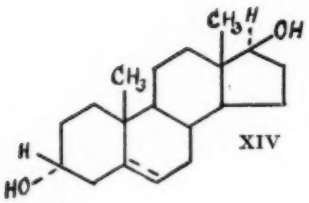
SOME UNSATURATED ANDROGENS



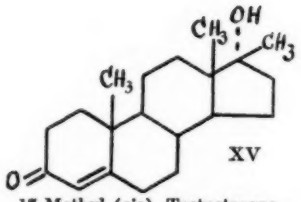
Dehydroandrosterone
(from men's urine)
(250—300 γ)*
(500 γ/10/16 mg.)†



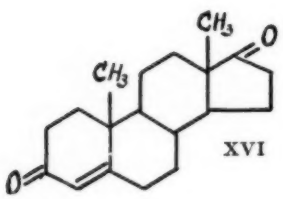
Testosterone
(from bull testis-tissue)
(13—16 γ)
(50 γ/10/150 mg.)



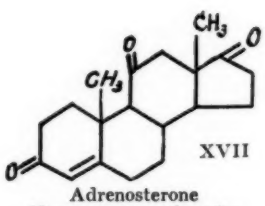
△
Δ^5-Androstenediol-3 trans, 17 cis
(not found in nature)
(235—650 γ)
(2000 γ no action in rat)



17-Methyl (cis), Testosterone
(not found in nature)
(10—15 γ)
(rat test?)



△
Δ^4-Androstenedione-3,17
(not found in nature)
(100—120 γ)
(100 γ/10/50 mg.)



Adrenosterone
(from suprarenal cortex
and from cortical hormone
by oxidation)
(500—600 γ)
(rat test?)

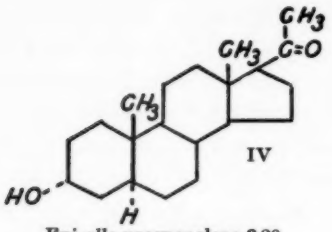
* equivalent of international unit on capon.
† per day for 10 days in rat with weight of seminal vesicle in milligrams.

17 are equally important in determining the potency. Please note that in the saturated and also in the unsaturated series the more active compounds have the OH groups in the *trans* position (indicated by – – bond) with reference to the nearer CH_3 group. Compare II and XIV with III and XI. A very striking example is testosterone which has been obtained in the *trans* and *cis* forms by Ruzicka and Kägi.[15] These authors report that the *trans* or natural form of testosterone is approximately thirty times as potent as the *cis* form also obtained by synthetic methods.

Of particular biological interest are epi-*allo*-pregnanolone-3,20 (IV) and adrenosterone (XVII). The former was first isolated from human pregnancy urine and thus accounts in part for the androgenic material found in pregnancy urine. It is interesting to note that an isomer thereof, *allo*-pregnanolone-3,20 (XIX) has been obtained from corpus luteum extracts, that two closely related compounds, pregnanediol-3,20 (XX) and *allo*-pregnanediol-3,20 (XXI) have also been found in pregnancy urine and that a third compound (XXII) has been separated from the urine of a woman afflicted with an adrenogenital syndrome.[16] The structural relations between these compounds shown on page 666 indicate that it is fairly safe to state that these substances probably represent waste products from progesterone secreted by corpus luteum tissue.

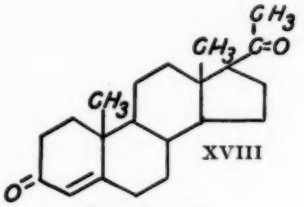
Adrenosterone (XVII) and pregnanetriol-3,17,20 (XXII) are of particular interest because their presence in the urine may reflect in part the cause for the hirsutism in certain cases of adrenal tumors and it also suggests that the adrenals may be responsible for part of the androgenic activity found in normal urines from men and women and especially from human castrates. The probable chemical relations between the adrenal cortical precursor, Kendall's compound E, and adrenosterone, are indicated by XXIII and XXIV. It is also obvious that XXII may possibly also be formed from compound XXIII and hence from suprarenal cortical tissue rather than from corpus luteum tissue.

This discussion leads us to the conclusion that at present six androgens have been found in nature and that four of them have been isolated from human urine. Only androsterone and dehydroandrosterone have been separated from men's normal urine. Whether all the androgenic activity from normal men's urine resides in these compounds or whether others contribute, remains to be determined. Although normal women also excrete large amounts of androgenic material, the exact nature thereof has not been determined. Thus far, no pure androgen has been



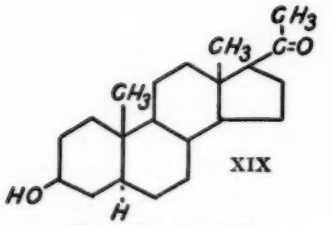
IV

Epi-*allo*-pregnanolone-3,20



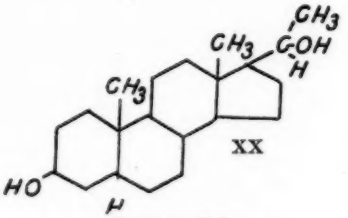
XVIII

Progesterone



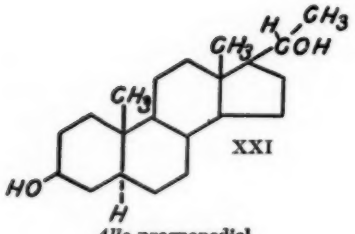
XIX

Allo-pregnanolone-3,20



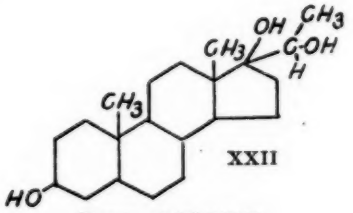
XX

Pregnanediol



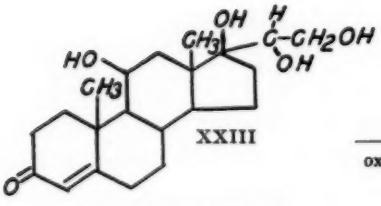
XXI

Allo-pregnanediol



XXII

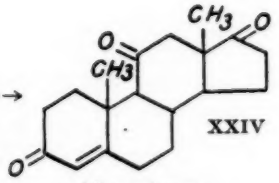
Pregnanetriol-3,17,20



XXIII

Kendall's substance E
from suprarenal cortex.

oxidation



XXIV

Adrenosterone

separated from the urine of a normal non-pregnant woman. However, in the pregnant woman, Marker, Kamm, *et al.*[17] separated epi-*allo*-pregnanolone-3,20 from the urine as one of the androgens. In pathological urines we undoubtedly have varying amounts of adrenosterone and pregnanetriol-3,17,20 in addition to androsterone, dehydroandrosterone, and many other possible compounds of androgenic character.

That the normal type of androgen may be increased in concentration in pathological conditions is well illustrated by Callow[18] who separated 110 milligrams of dehydroandrosterone in pure form from one liter of urine from a six year old girl afflicted with an adrenal tumor. This represented 70 per cent of the total androgenic material. In other words, this child excreted approximately 600 international androgenic units per liter of urine, whereas the normal child of that age might possibly excrete 2 to 10 units. In view of the possibilities of complex mixtures existing in various urines in various proportions it is very probable that future advances in the quantitative studies on urine will depend to a large extent on our ability to differentiate quantitatively between the different androgens. However, for the present we must be content with the estimation of the total androgenic activity in tissue, body fluids, and excretions in our attempts to correlate the quantitative information with various endocrine disturbances possibly involving the gonads. Our first consideration is the type of test animal to be used to give most reliable comparative analyses and the second the completeness of extraction of the tissues or fluids.

Complications involved in the rat seminal vesicle or prostate reaction to androgens. First it is necessary to present briefly the limitations of the rat assay method for comparative studies on crude concentrates from various sources. It may be recalled that in the early studies on concentrates Laqueur and his associates observed striking irregularities in comparing the results obtained by the rat method with those found by the capon comb-growth reaction. After the pure androgens were made available it became obvious that these irregularities are introduced mainly by the rat test. This was first clearly demonstrated by the Laqueur group[19] who discovered that a non-androgenic fatty-acid fraction ("X factor") from bull testis-tissue when injected with a given amount of testosterone increased the seminal vesicle weight response in the rat three to four fold over the effect of testosterone alone. The exact nature of the Laqueur "X factor" does not appear to have been determined, but

TABLE I

The influence of the daily injection of alcohols, fatty acids or esters on the response of the castrated rat to 10 daily injections of 50 γ testosterone

ALCOHOL, ACID OR ESTER	DAILY AMOUNT	NUMBER OF RATS	SEMINAL VESICLES	PROSTATE
	mg.		*mg.*	*mg.*
Sesame oil alone	0	3	14	41
Testosterone alone	0	4	42	66
Ethyl alcohol, C_2H_5OH	50	2	82	98
Propyl alcohol, C_3H_7OH	50	2	117	156
Propionic acid, $C_3H_6O_2$	50	3	117	158
Hexyl alcohol, $C_6H_{13}OH$	50	4	95	125
n-Hexanoic acid, $C_6H_{12}O_2$	50	4	95	140
Cetyl alcohol, $C_{16}H_{33}OH$	50	4	125	165
Palmitic acid, $C_{16}H_{32}O_2$	50	4	235	210
ω-Hydroxy palmitic acid, $C_{16}H_{32}O_3$	25	2	150	158
Stearyl alcohol, $C_{18}H_{37}OH$	50	4	200	220
λ-Hydroxy stearic acid, $C_{18}H_{36}O_3$	50	4	210	220
Ethyl propionate	50	2	33	66
Methyl stearate	50	2	43	89
Monostearin	50	4	40	76

Compiled from Miescher, Wettstein, and Tschopp, *Biochem. J.*, 1936, *30:* 1970.)

a number of pure substances can be substituted for the "X factor" and produce the same enhancing effect in the rat. Among these substances are aliphatic fatty acids, primary alcohols, hydroxy fatty acids, and estrogens. At least two substances have been found to decrease the seminal vesicle weight response. These substances are glycerol and paraffin oil. The decreased response with these vehicles for androgens might be attributed to too rapid absorption from glycerol and too slow absorption from paraffin oil to produce the optimum physiological response. This explanation does not seem completely satisfactory, however, because the addition of the proper fatty acids to these solutions increases the action of the testosterone three to four fold on the seminal vesicles. The data given in Tables I and II illustrate these statements. The mode of action of the fatty acids and primary alcohols is also by no means clear because only certain androgens are activated by these compounds. Among those not activated by the "X factor" or fatty acids are androsterone, urinary concentrates, androstanedione, 17-*cis*-testosterone, and testosterone acetate.

Esterification of testosterone also increases the potency of the prod-

TABLE II

The influence of the daily injection of various solvents on the response of the castrated rat to 10 daily injections of testosterone or testosterone acetate

	DAILY DOSE OF TESTOSTERONE OR TESTOSTERONE ACETATE	NUMBER OF RATS	SEMINAL VESICLES	PROSTATE
	γ		*mg.*	*mg.*
Sesame oil	0	3	14	41
Testosterone in sesame oil	50	4	42	66
Testosterone in 50 p.c. glycerol	50	2	16	46
	500	2	20	—
Same + 50 mg. ricinoleic acid	50	2	221	205
Testosterone in paraffin oil	50	2	15	44
Same + 50 mg. palmitic acid	50	2	126	145
Testosterone acetate in sesame oil	50	8	218	241
	200	2	383	357
Same + 50 mg. palmitic acid	50	2	210	279
	200	2	302	334
Testosterone acetate in 50 p.c. glycerol	50	2	12	36
	125	2	45	72
Same + 50 mg. ricinoleic acid	125	2	215	283
Testosterone acetate in paraffin oil	50	2	65	105
	200	2	252	293

(Compiled from Miescher, Wettstein, and Tschopp, *Biochem. J.*, 1936, *30:* 1977.)

uct. A given weight of testosterone propionate when injected into the young castrated rat produces three to four times the weight of seminal vesicle as is produced by the same weight of free testosterone. This enhancing effect of fatty acids, alcohols, and esterification is not manifest in the capon comb-growth method. In the capon method a slight delay in reaching the maximum comb-growth for a given dose may be observed with testosterone esters but this is not serious for the lower molecular weight fatty acids. For the higher molecular weight esters the response is very much delayed and of lower order. That is what one would expect because the dose of actual testosterone in a given weight of ester is diminished as the molecular weight of the fatty acid is increased. Table III and Fig. 4 give the experimental data for these conclusions.

The capon not only responds more quantitatively per molecule of androgen whether free or esterified, but also quantitatively the same to

TABLE III

Comparative assays of testosterone esters on capons

SUBSTANCE	DAILY AMOUNT EQUIVALENT TO ONE INTERNATIONAL ANDROGENIC UNIT OR = 100 γ ANDROSTERONE	TIME OF MAXIMUM EFFECT
	γ	*days*
Testosterone	15	6
Testosterone formate	20	7
Testosterone acetate	20	7
Testosterone propionate	20	9
Testosterone butyrate	60	12
Testosterone isobutyrate	70	13
Testosterone valerate	200	14
Testosterone isovalerate	250	15
Testosterone n-decanoate	350	16
Testosterone palmitate	>1000	—
Testosterone stearate	>1000	—
Testosterone benzoate	>1000	—

(Compiled from Miescher, Wettstein, and Tschopp, *Biochem. J.*, 1936, *30:* 1977.)

a uniform weight of testosterone whether with or without fatty acids or the "X factor."

From these experiences and many other observations it may then be concluded that at the present time the capon comb-growth response is a more satisfactory method for the quantitative assay of total androgenic activity in crude concentrates which are likely to contain various androgens as well as many other substances which may enhance or retard the response in the rat.

Quantitative studies on the distribution of androgens. We are now in a position to discuss the completeness of extraction of androgens and the possibility of androgens occurring in conjugated compounds in tissues and biological fluids.

Testis-tissue. Although the early reports, which were based on poor biological observations, led us to expect a relatively high concentration of hormone in testis-tissue, repeated attempts to increase the yield of androgen from bull testis-tissue by more extensive extraction or by hydrolysis of the aqueous phase before extraction by alcohol or benzene detect neither increases in androgen nor hydrolyzable conjugated forms thereof. The yield is practically the same as usually found by the routine McGee procedure and varies from three to nine international androgenic

units per pound of bull testis-tissue. If this is expressed in milligrams it calculates from 90 to 270 milligrams of testosterone per ton of tissue. It is of course still possible that a conjugation of an androgen with protein may exist and that we have not been able to break the hypothetical linking and still retain the activity. It is also of special interest that testis-tissue from calves and fetal calves actually yield higher amounts of androgens by the routine procedure. Why male hormone should be present in fetal testis-tissue in higher concentrations than in the mature animal is

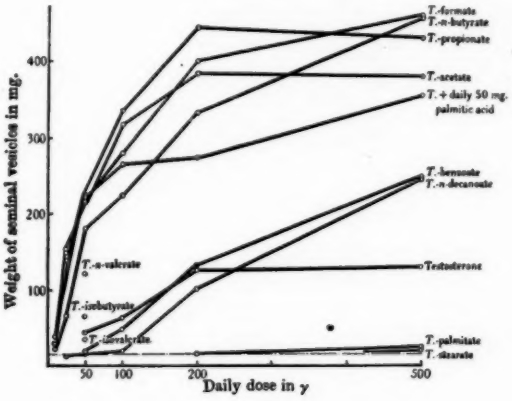


Fig. 4

rather perplexing. It seems to me that we must resort to the assumption that it is elaborated or stored in the organ but apparently not secreted in adequate amounts to influence the accessory sex organs.

Blood. The early claims for the high concentration of male hormone in blood also have not been confirmed. Recent studies by my associates* and myself also fail to detect a conjugated form of androgen in human blood. We had considerable difficulty in working up enough blood to warrant accepting the growth response as significant. We found it necessary to inject daily per capon for five days the equivalent of 136 cc. of human blood. Three different methods of extraction were employed on aliquots of the same mixture of blood with and without hydrolysis of the aqueous phase. We found four international units per liter of blood. This value does not seem unreasonable. If we assume, first, that the form

* In these studies as well as those on the aqueous phase from testis-tissue I am indebted to Messrs. Walter H. Hoskins, J. Robert Coffman, and George W. Beach for valuable assistance.

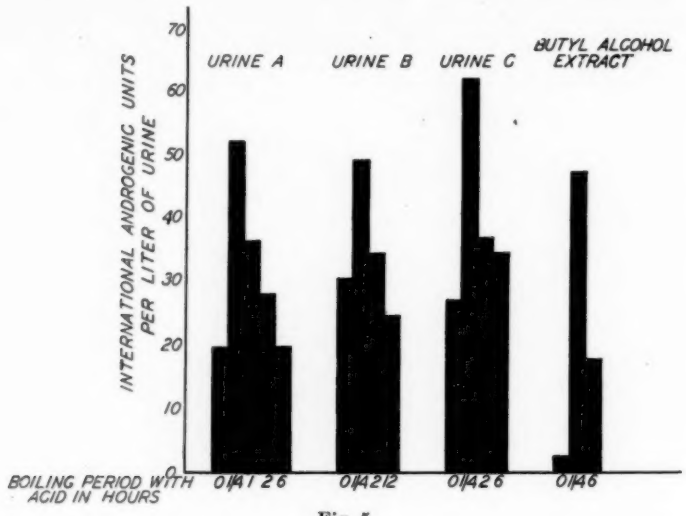


Fig. 5

of androgen in the blood is testosterone; second, that testosterone is converted into androsterone before it is excreted, and third, that the rate of clearance of blood by the kidney is 75 cc. blood per minute, the androgenic content of the 24-hour sample of urine should be 65 international androgenic units. The average amount of androgen in young men's urine is approximately 60 international units per 24 hours. If instead of assuming that all the testosterone is excreted as androsterone, we assume it is excreted as a mixture of androsterone and dehydroandrosterone with the activity in the urine equally divided between these two urinary androgens it would call for approximately 8.6 milligrams of the pure androgenic mixture. In these calculations we necessarily have made many assumptions and no claim is made as to the significance of the results. The values obtained are, however, interesting and suggestive.

Urine. The early assays on human urine gave values of 1 to 2 capon units (not over 4 international androgenic units) per 24-hour sample. With improvement in methods the yield was gradually increased until the values accepted at present for a normal man are 40 to 100 international androgenic units per day. The increased yields are due to more efficient extraction, to preliminary acid hydrolysis of conjugated forms, and to better control of destruction by the acid subsequent to hydrolysis. The

evidence for the existence of the conjugated form[20,21,22] and for the acid lability of part of the free androgenic material is given in Fig. 5. The first three pyramids show the effect of the length of time of acid hydrolysis at boiling temperature on the yield of androgens from raw urine. The last pyramid represents the effect of acid hydrolysis of the normal butyl alcohol-soluble but benzene-insoluble fraction obtained from freshly acidified unboiled urine. The urine which had been thoroughly extracted by butyl alcohol was boiled with acid and extracted with benzene in the usual way but the yield of additional androgenic material was negligible. It is evident that normal butyl alcohol is an excellent solvent for the conjugated form of urinary androgens, that practically all the androgenic material in urine is in an inactive water-soluble conjugated form, that acid hydrolysis yields the free form and that prolonged boiling with acid destroys considerable of the activity which was liberated in the first fifteen minutes of boiling. The conjugation appears to be of the hexuronide type. The gradual loss of activity with more prolonged boiling appears to be due to the destruction of dehydroandrosterone. We conclude therefore that androgens, like estrogens and decomposition products derived from progesterone, probably are excreted as hexuronides. Later investigations may demonstrate varying amounts of conjugated and non-conjugated forms in blood and urine and it is easily possible that such differentiation may be of considerable significance in determining diseased conditions. It may help in interpreting those cases in which abnormally high or abnormally low total values have been found without the manifestation of the expected physiological differences.

With our improved methods of extraction[20] we have accumulated considerable data on the urinary excretion of androgens in normal and abnormal men and women, in children and in various mammals. The results are tabulated below:

	INTERNATIONAL UNITS PER DAY	MG. EXPRESSED AS ANDROSTERONE
Men's urine (25-35 yrs.)	40–100	4–10
Women's urine (23-34 yrs.)	30–100	3–10
Boys' urine (6½ to 10 yrs.)	0.7–2.0/liter	0.07–0.20
Girls' urine (8-10 yrs.)	1.8–2.0/liter	0.18–0.20
Stallion	1–8/liter	0.1–0.8
Bull	<1/liter	<0.1
Ram	4/liter	0.4
Rat	<1/liter	<0.1

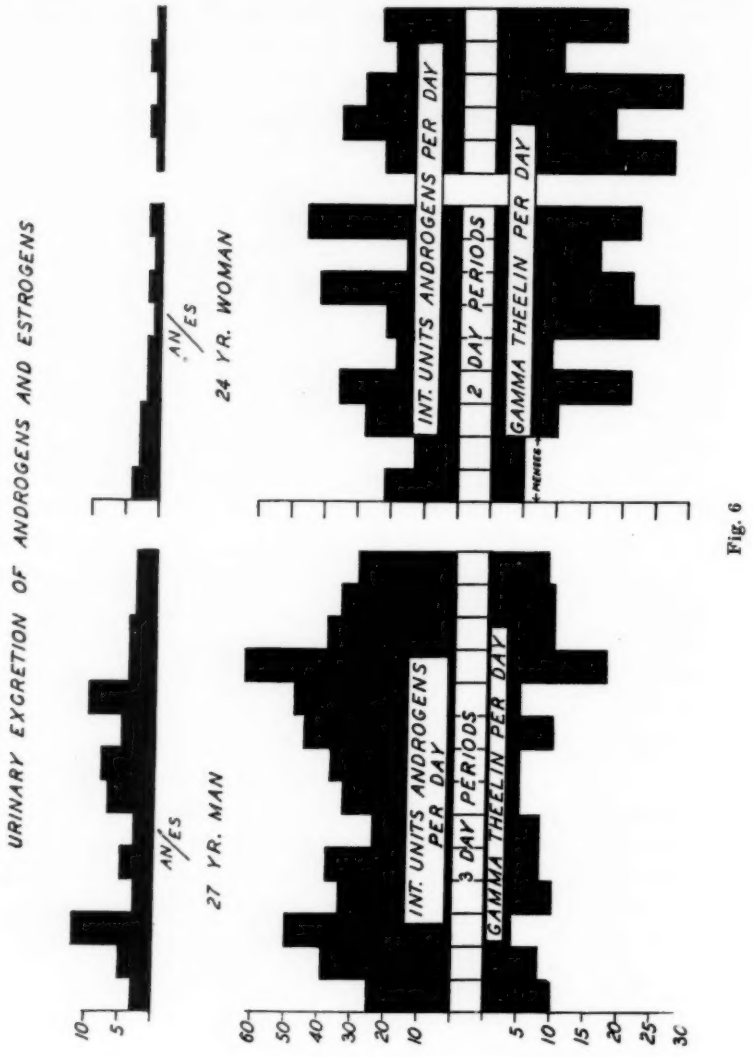


Fig. 6

It is evident that the excretion is exceedingly low in humans before puberty, but that adult men and women are unique in excreting large amounts of urinary androgen. These high values are all the more startling when we recall that Butenandt first separated only 15 milligrams of androsterone from the concentrate of 24,000 liters of human urine.

TABLE IV

The daily urinary excretion of androgens and estrogens in normal men and women

"An" designates international androgenic units per day. "Es" designates estrogenic activity expressed as gamma of theelin per day.

SUBJECT	AGE	TOTAL PERIOD	An			Es			An/Es		
			Max.	Min.	Ave.	Max.	Min.	Ave.	Max.	Min.	Ave.
		days									
1 ♂	27	42	63	24	38	18	4	9	12	3	4.2
2 ♂	26	42	65	27	41	20	2	9	22	2	4.6
3 ♂	30	44	79	13	41	29	2	10	22	1	4.1
4 ♂	35	36	65	23	40	21	5	12	6	2	3.3
Averages for men					40			10			4.1
5 ♀	34	27	42	17	25	40[2]	7	27	3	0.5	0.9
6 ♀	31	30	35	18	26	60[3]	13	36	2	0.3	0.7
7 ♀	24	30	46	13	28	28[4]	5	18	4	0.4	1.6
8 ♀[1]	23	31	85	42	56	41[5]	4	20	11	2	2.8
Averages for women (subject 8 not included)					26			27			1.1

[1] In this case the urine was boiled for 15 minutes with 10 p.c. HCl by volume before extraction by benzene. All other samples were boiled under the same conditions for 2 hours.

[2] 12th day after menses.

[3] 14th day after menses.

[4] 20th day after menses.

[5] 18th day after menses.

Today we should expect to find 15 milligrams of androsterone in four days' average collection of human urine. The reasons for the low yield of product by Butenandt are incomplete extraction, appreciable destruction, and the great difficulty in separating the pure androgen from the complex concentrate.

Variations in excretion in normal men and women. The systematic assays on complete collections of urine from men and women over periods of 27 to 44 consecutive days showed marked variations in the amount of androgens and estrogens excreted per day.[20] Fig. 6 shows these fluctuations in a man and in a woman. The minimum, maximum, and average values found for the four men and four women are given in Table IV. It should be emphasized that these analyses required pooling the collections into 2- to 4-day samples in order to obtain enough material for accurate assay purposes. In other words, the daily variations as given are already

averaged and therefore it is easily possible that the actual daily excretions are over a still greater range. These variations in normal men and women should serve as a warning not to place too much emphasis upon the assays on one or two 24-hour samples of urine. Furthermore such amounts of urine are of doubtful value because the assay is likely to be based on too few capons. Inasmuch as tremendous variations do occur normally it is much wiser to average these results and increase the accuracy of the assay by extracting large volumes of urine preferably representing more than 3 days' complete collection.

In studying Table 4 it should be observed that the analyses of the urine from subject 8 were carried out after hydrolyzing with acid for fifteen minutes instead of for two hours as was the case with the other seven subjects. This accounts for the high yield of androgens in this case. A number of comparative assays carried out on urines after fifteen minutes' and two hours' boiling with acid have shown that the former procedure leads to an increase of 66 per cent over the latter in androgenic units. If we assume that this increase would have been observed in the other seven subjects the average daily excretion of international units of androgens would be sixty-six for the men and forty-seven for the women and the average An/Es ratios would be 6.9 for men and 2.0 for women instead of 4.1 and 1.1 as given in the table. It appears that the sex differences in the ratios are due more to a lower excretion of estrogens than to a higher excretion of androgens in men. Attention should again be called to the striking daily variations in the An/Es ratios in each individual. In other words, there does not appear any correlation in the excretion of androgens and estrogens in men and women. However, the women always excreted the lowest amounts of estrogens during menstruation and also tended toward a lower level of excretion of androgens during this period. In the women the highest excretions of estrogens were observed on the 12th, 14th, 18th, and 20th days after the menses, but this was not uniformly associated with a rise or fall in the excretion of androgens. Although Fig. 6 suggests a definite cycle of androgen excretion in the male, this is not uniformly true.

The origin of the urinary androgenic and estrogenic substances in these normal men and women is no doubt mainly from the gonads. There is no evidence that changes in diet are likely to affect the excretion rate of the sex hormones. However, other organs and particularly the suprarenal glands may normally yield products which possess androgenic

TABLE V

The urinary excretion of androgens and estrogens in hypogonadism

"An" designates international androgenic units per day. "Es" designates estrogenic activity expressed as gamma of theelin per day.

NUMBER OF PATIENTS	TYPE	AGE RANGE	An			Es			An/Es		
			Max.	Min.	Ave.	Max.	Min.	Ave.	Max.	Min.	Ave.
4	Cryptorchid	13–36	31	9	16	6	1	3	31	0.8	2.8
5	Eunuchoid	23–36	17	0	11	2	1	1.7	17	0.5	8.0
2	Castrate	21–56	3.5*	1*	2	4.5*	3*	3.8	0.8	0.3	0.5
4	Gynecomastia	15–24	37	0	15	15	5	11	2.5	1.6	2.0
4	Normal men	26–35	79	13	40	29	2	10	22	1	4.1
4	Normal women	23–34	51	13	28	60	28	27	7	0.3	1.2

* Per liter.

activity. These products may be one or more of the pure substances separated from pathological urines or they may be precursors formed by the adrenals for conversion into sex hormones in the gonads.

Urinary excretion of androgens and estrogens in hypogonadism and virilism. In cooperative investigations with Dr. A. T. Kenyon of the Department of Medicine at the University of Chicago we have applied our methods of assay on urines from subjects with various endocrine disturbances.[23] Table V presents a general summary of the results in hypogonadism in the male. In cryptorchidism we observe consistently low rates of excretion of androgens and estrogens and an average low ratio as one might expect. In eunuchoids the excretion rates are still lower with a remarkably high average ratio. In gynecomastia the androgen excretion rate is of the order observed in cryptorchidism but the estrogen excretion is more of the order found in normal men and, as a result, the ratio tends toward the normal female type. In male castrates the rate of excretion of androgens is particularly low, but the change in the rate of excretion of estrogens from the normal is not of the same order. As a result the ratio values are even lower than in normal women. In short, from these limited observations we may arrive at the tentative conclusion that the absolute amounts of androgens as well as the ratio of androgens to estrogens determine the type of hypogonadism.

Table VI presents a general summary of the results obtained in virilism. In the subjects for whom the diagnosis indicated normal adrenals, the relatively normal excretion of androgens appears to be associated with

TABLE VI

The urinary excretion of sex hormones in virilism

"An" designates international androgenic units per day. "Es" designates estrogenic activity expressed as gamma of theelin per day.

NUMBER OF SUBJECTS	TYPE OF ADRENAL	AGE RANGE	An			Es			An/Es		
			Max.	Min.	Ave.	Max.	Min.	Ave.	Max.	Min.	Ave.
7	Normal adrenals	13–32	44	5	26	19	6	13	3.0	0.2	2.3
2	Adenoma	31	8*	0*	4*	10*	4*	7*	0.8	<0.25	<0.5
2	Carcinoma	16–36	480	69	—	8	—	—	60	—	—
4	Normal women	23–34	51	13	28	60	28	27	7	0.3	1.2
4	Normal men	26–35	79	13	40	29	2	10	22	1	4.1

* Per liter.

a lower level of estrogen excretion and hence a ratio approximately twice that of normal women. In the two cases of adrenal adenoma the very low excretions of androgens and an excretion of estrogens even lower than in normal men are very striking. In both cases of adrenal carcinoma the androgen excretion is remarkably increased and the estrogen excretion in the one case again is lower than in normal men and hence the very high ratio. Possibly one may conclude tentatively that in women, hirsutism is not necessarily associated with abnormally high excretion rates of androgens, but that it may also, even at very low rates of excretion of androgens, be associated with a low rate of excretion of estrogens. It is, however, also possible that androgens of different types act quite differently quantitatively in influencing hair distribution and in comb-growth stimulation respectively. It is also possible that the product responsible for some types of hirsutism may be so altered before it is eliminated by the kidneys that some of its supposed androgenic action is lost.

In summary we may conclude:

1. That at least six androgens have been obtained in pure form from human urine and animal tissues.

2. It is generally assumed that testosterone is the true male hormone elaborated by testis-tissue, although it is possible that different species may elaborate other forms of androgens.

3. The normal urinary forms of androgens in men are androsterone and dehydroandrosterone.

4. It is generally assumed that these may be derived from testosterone.

5. Androsterone and dehydroandrosterone are not excreted in the free and physiologically active form, but probably as glycuronides.

6. These inactive forms are easily converted into the free androsterone and dehydroandrosterone by acid hydrolysis.

7. Pure androgens have not been separated from normal women's urine, hence the exact nature is not known.

8. Although quantitative studies on urines from normal and abnormal men and women reveal differences in the absolute and relative rates of excretion of androgens and estrogens the data obtained are not as striking as one might have expected.

9. Androgens other than testosterone, androsterone, and dehydroandrosterone have been obtained in pure form from human urine in cases of hirsutism.

10. Some of these new forms of androgens may be formed in the adrenals at abnormal rates at times.

11. It is very probable that the quantitative differentiation between various forms of androgens will help to explain some of the apparent discrepancies we now observe in diagnosis and urinary assays respectively.

12. Finally one probably can not apply Krogh's statement, "I do not trust my reason in physiology five minutes away from the facts" more truly in any other field in endocrinology than in the one under discussion here.

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THE MANAGEMENT OF HYPERTENSION*

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WHEN I was invited to give this lecture on "The Management of Hypertension", I wondered whether the choice of title was a happy one, first, because there seemed to be little that one could add to what was already in the literature; and second, because no matter how much "management" one undertakes, the natural history of the disease seems to run its course undisturbed. Yet when I thought more about the invitation, I came to welcome the opportunity of crystallizing my own experience against the background of hypotheses and accepted facts relating to this syndrome. Furthermore, there is one point of view in the management which I want to emphasize, for there is little mention of it in textbooks and in the literature. I shall return to this shortly.

The so-called degenerative diseases are taking on added significance since the increase in the life span of man has been secured by decrease in the death rate due to infectious diseases. Dr. Cohn[1] first directed attention to the fact that the apparent rise of the death rate in heart diseases was to be accounted for by its increase in the later decades, in short, in the degenerative age-group; the individual having been spared from typhoid fever or diphtheria for instance, must eventually die, and in a great number of these, the heart finally fails. As this greater number of individuals are permitted to attain an older age and as they grow older, parts of the organism begin to break down; perhaps those parts give way first which have been subjected to injury in the individual's life history, or it may be those parts to which weaknesses may have been contributed by our forebears. The social security program indicates a burden on those in earlier decades to provide for those whom our medical progress has given added years. We are obligated, therefore, to look ahead to see how we can make this older age group useful members of society and economically self-sustaining, if possible; and at the same time guarantee

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them health during this period. In this connection, hypertension is important since it is one of the forerunners of heart disease in middle and later life.

I have chosen to restrict my discussion to what is commonly called essential hypertension, which I shall abbreviate further to hypertension. This designation will at least provide us with a diagnostic rubric. Moreover, I wish to limit my discussion to hypertension *per se* and its consequences without considering arteriosclerosis. We observe cases of hypertension before vessel changes are detected clinically. What changes in the kidneys there may be at this stage are at present not known. After hypertension has been present for a period of time, however, vessel changes occur and arteriosclerotic alterations are detectable. There are accordingly individuals in whom arteriosclerosis and hypertension are interrelated, and yet another group in which they may be coincident or independent phenomena.

In the treatment of disease, we can more often make greater advances when the etiological agent or factor has been discovered. In the case of essential hypertension, the etiology is still not known. There is a variation of opinion about the criteria for making the diagnosis which is further complicated by the different levels at which blood pressure readings are made, as well as the practice of recording blood pressures with the patient sitting up and lying down. Insurance companies are keeping alive the tradition of taking "sitting" blood pressure since their statistics have been compiled on this basis. Moreover, the width of the cuff, a factor which is again receiving attention, may influence the blood pressure reading. Also, different levels may be read by two observers using a stethoscope with two ear-phones. All these factors make little difference in the established, easily recognized, case of hypertension but they are important considerations in the borderline case and in evaluation of therapeutic procedures. It is apparent also that they vitiate results relating to incidence.

In most clinics, a diastolic level of 90-100 mm. of mercury is accepted as the criterion for the upper limit of normal. The practice of taking resting-lying blood pressure should be encouraged, for this postural factor can be controlled for comparison in subsequent observations. A record of the sitting blood pressure may be made as well, if there is reason to have this information. It is good practice to take the blood pressure at a stated time in the course of the physical examination, after

the patient is at ease, and has been lying down ten to fifteen minutes, while the examiner is proceeding with the rest of the examination. Moreover, we should seek uniformity about the systolic and diastolic levels, namely, the systolic when sounds are first heard, and the diastolic when the loud sound changes to a murmur. If this cannot be detected, the level at which sounds disappear may be read and 5 mm. added to it. Hypertension should be diagnosed only after elevation of the blood pressure has been recorded on several occasions.

That the etiology of hypertension has not been solved, probably accounts for studies being made from so many points of view. Let us look into some of these, for they will give us a better understanding of what we may hope to accomplish in therapy. First, what is the incidence of hypertension in the population?

It is not a matter of surprise that our notions about this particular point are inaccurate, partly because of variations in recording but also because hypertension occurs asymptomatically. It is discovered in most patients when they begin to have symptoms. In certain ones, however, it is detected in the course of examinations for life insurance; in others in the routine physical examination which a few people in the total population make use of as a health precaution; and finally, in still others who come under observation because of another malady. The reasons therefore for inaccuracies about the date of onset of hypertension, about its duration, and about its age distribution are apparent. Moreover, when we come to analyze the population of cardiac clinics, it appears that these patients are not followed over as long periods as patients in the rheumatic group.

What are the estimates of the incidence of hypertension? Allan[2] states that 40 per cent of the population above the age of sixty years exhibits hypertension. In the available statistical data relating to this point there appears to be more or less agreement that the incidence rises gradually up to forty-five years, after which there is tremendous increase in the decade from forty-five to fifty-four years and sudden falling away after seventy years.[3] Approximately 60 per cent of the cases occur in the forty-five to sixty-nine year period. The steep rise occurs five years sooner in women than in men, and is roughly about twice as frequent in women as men. The age of incidence suggests involutional changes as an etiological factor.

Most investigators seem to agree concerning the hereditary back-

ground of hypertension, not alone when the analysis is made from the positive point of view of the high familial incidence of hypertension in those exhibiting hypertension, but also, negatively, when one considers the low incidence of hypertension in other familial groups.[4] We are too strongly convinced of this notion to have it altered by Allan's analysis purporting to contradict it.[2] We are all impressed by the greater number of cardiovascular accidents in hypertensive families. Hines[5] contributes confirmatory evidence obtained in another fashion. He made the so called cold pressure test, the rise in blood pressure when the arm is placed in cold water, in the families of hypertensives. He found that the family history of hypertensive cardiovascular disease was five times more frequent in individuals with hypertension or "hyper-reactors" than it was in those who reacted normally to the test.

The racial and environmental distribution of the disease are of interest. The infrequency of hypertension in the Chinese is an accepted fact and foreigners living in China have been found to experience lowering of the blood pressure.[6] In urban Japanese, however, hypertension is almost as common as in Americans and in Europeans.[7] Hypertension is not found in Africans in their native habitat, but it is even more prevalent in negroes in the United States than in the white population. These facts lead to the opinion that the incidence of hypertension is related to the environment in which the individual lives.[8]

It may be stated in passing that many hypertensives are obese, but this does not appear to be the controlling factor.

The psychologic side of hypertension, as well as the constitutional panel of hypertensive individuals, will be considered shortly.

We now come to the nature of hypertension. It is agreed that the rise in diastolic blood pressure in hypertension is a consequence of increased peripheral resistance, especially in the arterioles—the precapillary portion.[9, 10, 11, 12] Whether increase in peripheral resistance is due to hormonal (including chemical) changes, or to nervous control is still awaiting solution. The observations of Prinzmetal and his co-workers[11] and of Pickering[13, 14, 15, 16] put stubborn facts in the way of acceptance of the nervous control mechanism; and yet, on this concept depends the rationale of the surgical treatment of hypertension which is now receiving wide attention. There is a vast contradictory and controversial literature relating to the two points of view, the hormonal and nervous regulation. The carotid sinus does not appear to be implicated, since its behavior

is the same in the hypertensive as in the normal subject.[17]

A new approach to the study of hypertension was initiated by Goldblatt[18, 19] in the production of hypertension by renal ischemia induced by the application of constricting silver clamps to the renal arteries of dogs. The means by which rise in blood pressure is achieved under these conditions has been widely studied in the light of the nervous and chemical origin. Although the matter is unsettled, the balance of evidence, at present, is in favor of a renal-humoral nature. What the final implications of Goldblatt's highly important observations will be, as well as of those growing out of his approach, cannot be stated at present; nor is it possible to assign them a proper rôle in the interpretation of the etiology of clinical hypertension in man.

Let us inquire a moment into the pathological physiology of hypertension. Again we find that studies have been made from many points of view. And indeed this is inevitable since its effects are widespread. We may enumerate certain of them briefly. It has been found that the velocity of blood flow (measured clinically as circulation time) may be normal, or may be slightly decreased in the absence of heart failure. It is significant that it is not increased.[20]

Steele's[21] observations show that pulse wave velocity is increased in hypertension, and that it is related to the diastolic level and not to the pulse pressure as was Weiss' notion.[22]

It is well known that there are certain cases of hypertension having small hearts and others having large ones. Starr has contributed data leading to definition.[23] He found that those with small hearts had a smaller basal cardiac output than those with large hearts. In certain ones the cardiac output was smaller than in subjects with normal hearts. This reduced cardiac output achieves the maintenance of hypertension without increase in the heart's basal work. When the basal cardiac work is not elevated, the heart is not enlarged. When it is elevated, the amount of enlargement is closely proportional to the increased work. Therefore, cardiac enlargement in analogous to that which occurs in skeletal muscle after increased work. It appears that the failure of cases with prolonged hypertension to develop cardiac hypertrophy may be attributed to the reduced cardiac output and it has been found that they show no hypertrophy at autopsy examination. Clinically, cardiac decompensation is less likely to occur in cases of hypertension with small hearts than in those with large ones. As we have stated, the arterial pressure is increased

but the venous pressure is not elevated unless cardiac failure is present.

Early, the electrocardiogram is usually normal, but later it may show certain alterations. There may be left axis deviation which will usually indicate preponderance or hypertrophy of the left ventricle. When T wave changes occur, they may be associated with the hypertension *per se* or may indicate that changes in coronary vessels have occurred.

The basal metabolic rate may be normal in hypertensive subjects.[24] The viscosity of the blood and the blood volume do not differ significantly from normal.[22]

Steele[25] has shown that the skin temperature of persons with hypertension does not differ from normal individuals and that variations in it occur without change in blood pressure. Elevation of blood pressure in persons with hypertension does not primarily depend then on constriction of the arterioles of the skin.

We come now to the renal physiology. The tests of renal function, namely, urea clearance, the phenolsulphonphthalein excretion, and the limits of concentration and of dilution may all be in the normal range in the presence of hypertension.[26] The chemical constituents of the blood, for example urea, chlorides,[27] and cholesterol,[28] may show no alteration. Nor is there indisputable evidence that this blood has unusual quantities of pressor substances.[29] After the persistence of hypertension, however, changes in renal fuction usually occur. It is not known whether there is a time factor. It has been found that the urea clearance test detects impairment earlier and is more sensitive than the others. The phenolsulphonphthalein excretion is the least sensitive test. Changes in plasma proteins, and in the red blood cell count and hemoglobin of the blood occur only late, if at all. Addis' sediment counts may at first show no alteration in the number of formed elements. Later, however, changes may be detected.

When a patient comes under observation, how can we evaluate his condition?

First: With respect to the functional capacity of the heart, the best guide is the patient's own history of how much can he do with or without symptoms, data which are best ascertained by listening to a detailed account of a day's activities; and finally what signs of failure does the patient exhibit.

Second: The following examinations aid in evaluation of the state of the kidneys: (1) the urea clearance and the blood urea; (2) the range

of the specific gravity of the urine in concentration and dilution tests; (3) the phenolsulphonphthalein excretion, if the urea clearance test is not available; (4) the sediment of the urine, and perhaps the Addis count; (5) the albumin excretion in the urine.

Third: Anatomical changes may be disclosed by the following procedures. Examinations are made to determine the state of the peripheral vessels; the eyegrounds for vessel changes–papilledema, hemorrhages; an x-ray of the heart for its size; an electrocardiogram to discover axis deviation and coronary artery changes.

Fourth: The level of the blood pressure should be determined. The diastolic level is the more important. I prefer to see a patient with a labile blood pressure than one in whom the level is fixed. It is well known that patients may exhibit for years high systolic blood pressure without revealing any of the changes mentioned above.

Fifth: Inquiry should be conducted to gain an insight into the personality of the patient for the help it contributes in therapeusis.

The clinical course of hypertension is not accurately known because of its insidious onset without symptoms and because patients may not be observed carefully until they show evidence of strain on one of the systems.

What may be the course of events in patients who exhibit hypertension? In the first place, they may live their life span and suffer an intercurrent disease. In the second place, the predominant damage and strain may be cardiac from which they develop congestive heart failure. The failure is occasioned in a great majority of cases by coronary artery sclerosis or it may be subsequent to coronary thrombosis. Congestive heart failure is the most common cause of death of patients with hypertension. From another point of view, hypertension is the most common cause of cardiac affections in persons over fifty years of age, one quarter of all deaths being due to it (Averbuck[30]). In the third place, as I have already mentioned, they may suffer coronary occlusion with the course of events that this implies. In the fourth place, certain others suffer renal changes and renal death is their lot; and finally, others experience cerebral vessel changes and cerebral accidents.

Flaxman[31] has analyzed a series of 623 cases, 189 of which were dead and 434 known living. Eighty per cent of those who have succumbed died two years after onset of symptoms; 65 per cent of those dying, died of congestive heart failure; congestive heart failure occurred most

frequently one year after symptoms appeared and 85 per cent died one year after the incidence of heart failure; 64 per cent of negroes died before fifty years of age; but only 30 per cent of white sufferers died before fifty years of age; a few were living five to twenty years after the first appearance of symptoms, and a few were living five to eight years after onset of congestive heart failure.

Patients may live many years though the systolic level is high, but the diastolic level is more important in prognosis, and lower diastolic levels favor longevity. Good renal function is a favorable sign. Moderate cardiac hypertrophy is not unfavorable, but large hearts are more likely to fail than small ones.[32] Women appear to tolerate high blood pressure better than men. Cerebral accidents, anginal attacks, and retinal hemorrhages are unfavorable signs.

In passing, there is one situation in which hypertension appears to be of benefit, namely, in the presence of mitral stenosis. It was Levine's and Fulton's belief[32] that the favorable influence on the natural history of this valve lesion is achieved by the enlargement of the left ventricle and dilatation of the stenotic ring which hypertension encourages.

I should like to discuss heart failure briefly. Hypertensive patients suffer several types of failure. First, they may experience paroxysmal rises in blood pressure, the so-called vascular crises, which may be attended by acute heart failure. Second, they may exhibit acute cardiac dilatation with pulmonary edema. Finally, they may sustain the sequence of events recognized as chronic congestive heart failure. For the relief of the first, the liberal use of morphine is indicated. It has been found that adrenalin may give them rapid relief, and results, not in further rise in blood pressure, but in its fall. Aminophyllin intravenously may be used. In the treatment of pulmonary edema, morphine is invaluable. I do not resort to venesection unless the patient's condition is very urgent. Digitalis in full therapeutic amounts is given by mouth or rectum. I do not subscribe to the use of hypertonic glucose solution, for it draws fluid from the tissues into the blood stream, adds to the volume of the circulating blood, which in turn increases the load on the heart.[33] Oxygen therapy may be instituted and may be given under positive pressure as recommended by Barach.[34]

When congestive heart failure occurs, it has the usual signs and symptoms associated with failure and needs no special comment. The changes in the circulation are similar to those occurring in patients

suffering failure from other causes, such as rheumatic heart disease, namely, decrease in cardiac output per minute and per beat, rise in venous pressure, and slowing of circulation time, and the work of the heart per beat is not commensurate with the heart size.[35, 36, 37, 38] The giving of digitalis results in decrease in size of the heart, increase in cardiac output, fall in venous pressure and shortening of the circulation time, and the work of the heart is increased per beat and the heart now smaller, the work is more nearly commensurate with the heart size.[35, 36] The treatment of heart failure in hypertension is the same as in other etiological types; namely, (1) the use of digitalis in full therapeutic amounts; (2) low salt diet; (3) restriction of fluid intake; (4) xanthine drugs, such as theocalcin by mouth, and aminophyllin by mouth or intravenously; (5) one of the mercurials intravenously may be required. Mercupurin, a mercurial combined with theophylline, has, in my experience, been the most valuable of this group for the mobilization of fluids.[39] Renal function does not appear to be impaired by its use and it may be given if hematuria is not marked.

During failure, the blood pressure rises in certain patients and falls in others and seeks its usual level as restoration of efficiency occurs. Mention may be made also of the fall in blood pressure which occurs in coronary occlusion. Since the blood pressure may remain low after recovery, in the evaluation of a case seen at this time, it may be helpful to ascertain the history of preceding hypertension.

The symptomatology of hypertension is not clear. The experience is common that patients suffer no symptoms until by chance hypertension is discovered, after which they have many complaints. Moreover, what symptoms are due to hypertension *per se* and what to the "complications", are not separable from the records now in use. Certain analyses have indicated that hypertensive symptoms are psychogenic in origin.[40, 41, 42] The symptoms, whether related to hypertension *per se* or its complications, or whether psychoneurotic in origin, are too well known to enumerate. Analysis of the symptoms, as they have been recorded in the past, does not give a clear insight into their origin and nature.

We come now to the treatment of hypertension. I shall speak first of drugs. I am of the opinion that none of the drugs directed toward lowering blood pressure are of benefit. In testing any procedure it must be kept in mind that the effects are difficult to evaluate because of expected

fluctuation in blood pressure and of relief of patients when they are given any kind of medication.

Gager[43] has recommended the use of potassium sulphocyanate, to be given 0.1 gm. three times a day after meals for one week, then twice a day for one week, then once every day for one week, and then every day or every second day. The attempt is made to keep the level of cyanate in the blood at 10 mgm. per cent, since toxic symptoms occur when it is 15 to 30 mgm. (psychosis, dermatitis, cardiac pain[44, 45]). In certain patients, fall in systolic and diastolic blood pressure and relief of subjective symptoms occur. I have not had much success with its use.

Bismuth subnitrate may be given for the nitrite effect, in 0.6 gm. amounts three times a day. Bruen[46] is of the opinion that it gives no greater fall in blood pressure than the usual variation which is encountered. There is danger of cerebral accidents from its use.

Erythroltetranitrate in 0.03 gm. doses may be given. I have not had occasion to use it for some years.

Of the tissue extracts, lacarnol is the only one I have tested. I can attribute no significant benefit to its use.

The salt free diet has enjoyed a vogue, but too much has been claimed for it. Under well controlled conditions, fall in blood pressure occurs in certain patients and they experience fewer symptoms on the regime, and are on the whole more comfortable. Universal success, however, is not to be expected. I usually follow the practice of recommending a low salt diet.

The place of luminal and barbiturates in the management of hypertension will be discussed later.

We come now to the place of surgery in the treatment of hypertension, a pertinent question at the moment. Hypertensive patients and the lay public are hearing too much about it through pseudo-scientific writings and the newspapers. It raises a hope in them which, at the present time, is not justifiable. It would be unfortunate to subject great numbers of individuals to this therapy under uncontrolled conditions until a number of well controlled cases have been observed for a sufficient time to permit its evaluation and to establish its effect on the life histories of those treated. Our analysis made in the earlier part of this discussion, makes apparent the difficulties inherent in such an evaluation. Time will not permit a detailed discussion of the various surgical procedures, nor is it profitable for us, in view of the fact that the part it plays at the present

time in the management of the hypertensive patient must sanely be restricted to a few selected cases. Everyone subjected to therapy should undergo thorough evaluation beforehand in the manner we have indicated. The recent literature has many papers recording the experience of those who have explored this field.[47, 48, 49, 50] Dr. Heuer[51] has recently summarized his and Page's experience. The operation of division of the anterior nerve roots of the spinal cord from the level of the sixth dorsal to the second lumbar vertebrae level resulted in fall in systolic and diastolic levels of blood pressure, regression of retinal changes, and improvement in subjective symptoms in a sufficient number of patients to encourage this approach. In certain ones, the blood pressure rose again later. The operation itself is associated with real dangers which are cause of concern. Again, splanchnic resection in Heuer's experience was associated with fall in blood pressure, relief of subjective symptoms, and regression of retinal changes, but the blood pressure rose to the preoperative levels in all patients in six months.[49] Dr. Heuer and I are expanding this series of patients in order to observe further the possibilities of this procedure. Those patients who have exhibited improvement following one of the surgical procedures, encourage the continued exploration of the application of surgery to this province, but what place it will eventually take and which of the procedures will prove to be the most beneficial cannot be foretold at this time. Too wide use should not be encouraged for fear it will fall into disrepute before its usefulness has been established.

How does one "take care" of a patient suffering from hypertension? Much of what we do should be directed toward an understanding of the individual who has the disease. By and large, they have increased psychomotor activity, they are dynamic hyperactive individuals, they are sensitive, quick tempered, yet they have certain differences from the manic depressive groups which they may simulate, for they are not moody and are not the "up and down" type. Ayman and Pratt's analysis shows that hypertensive symptoms are of psychic origin.[42] There is still the difficulty in deciding whether the patient is this type of person because he suffers from hypertension or whether he develops hypertension because of this individual type. Extensive studies have not been made to discover whether there is a constitutional panel,[52] morphological and physiological, of hypertension such as Draper[53] has described for gastric ulcer or gall bladder disease.

Since no specific drugs nor certain surgical treatment are avail-

able for the hypertensive subject, we must resort to the lines of symptomatic therapy. Having evaluated the patient's anatomical lesion and functional capacities, how do we take care of him? First, what is the general regime? (1) No special diet is indicated, but it should be a well balanced one. Protein should not be restricted, first, because it has been shown that it is not a factor in production of hypertension, and second, its limitation may lead to plasma protein depletion and favor the onset of edema. Salt may be limited to that used in cooking but highly salted foods are prohibited and highly seasoned ones eliminated. (2) If the patient is overweight, the caloric value of the diet should be reduced, without deprivation of essential factors. (3) Regular bowel habits should be established. (4) The use of tobacco should be eliminated. There is no evidence that tobacco is of benefit while there is some pointing to its harmful effects. This point of view is discussed frankly with the patients to prevent disappointment. (5) The moderate use of alcohol is countenanced because of its vasodilator effect. (6) Strenuous sports are discouraged, but the patient may indulge in less active games. Each case must be inidividualized. (7) Luminal is one of the most useful drugs in the care of the hypertensive individual. It is prescribed for the relief of persistent headache or to lower the level of hyperactivity. It may be given over long periods of time. (8) If hypertension has appeared at the menopause, an ovarian extract may be useful.

In the regime of persons with hypertension, the excesses should be eliminated; they must not overwork, nor overeat, nor undersleep, nor oversmoke. Measures are directed at relaxation and attaining mental ease. Part of this is secured by psychotherapy and part by re-training the patient by his own efforts. Plans should aim at lowering the pace at which the patient lives and toning down his reactions to his environment. The patient must acquire a different pattern of living. How can these objectives be attained?

First, one should try, without engendering fear, to encourage the patient to take the attitude that it is better to lead a slightly restricted life over a long period of time than incur long invalidism. Second, hot baths at home and occasional visits to Spas for the "cure" may be helpful. Whether lowering of blood pressure to the extent that is claimed at the Spas occurs, I am unable to say; nevertheless, certain patients are symptomatically benefited by the regime. Third, long hours of sleep should be indulged in. Fourth, relaxation periods during the day may be

in order. Executives may have a couch in the office and lie down after lunch. Fifth, frequent short vacations away from business worries may be possible. Sixth, remove worries, if it is possible. It may be expedient to remove certain patients from one business to a less disturbing one, or from one department to another. Seventh, the organization of the home life should be scrutinized. Eighth, relaxation at night without night work is essential. Ninth, exposure to the hot sun should be avoided. Tenth, if the patient is not aware of the rise in blood pressure, it may be best not to discuss it with him, but with a member of the family. Eleventh, the patient should be reassured about his blood pressure, and given the bright side of longevity; he should be told something about the rationale of therapy. Twelfth, the patient should be encouraged to acquire a hobby. Finally, in the direction of psychotherapy: The best results will be secured by listening to patients' troubles and, if it can be done, rearranging lives. This takes a great deal of the physician's time, but it appears to me from my experience to be the best therapeutic measure we have at our disposal. It is a side of the therapy that is not usually recognized, and if recognized, not given proper emphasis nor adequate attention. For the most part, these patients do not need psychotherapy in the usual sense of the word, nor do they need to be transferred to the care of a psychiatrist. As a matter of fact, harm may be done to certain patients if the latter course is pursued, because of the present implications to the patients of having psychiatric care, and because something is lost, so far as patient and doctor relationship is concerned, by transferring the patient from your care to someone else for this phase of therapy. I should like to encourage attention to this phase of the management. From the psychotherapeutic standpoint, no problem in their lives can be too trivial for them to bring to the physician, since it may be the trivial problems that they magnify into great ones. Their state is very susceptible to improvement by encouragement. The exacting care which this kind of treatment necessitates is hard on the physician, but is a responsibility which we must assume.

On the other hand, I have emphasized that they must be encouraged to stand on their own, and they must be re-trained and induced to moderate their lives. Jacobson[54] has made contributions in this direction by the technique which he calls "Progressive Relaxation." It has as its objective, the training of individuals to relax and to eliminate "tensions". The methods involved are somewhat too tedious for brief exposition.

Careful scrutiny of his physiological studies and of the description of the techniques employed, convince me that a new approach has been opened in the therapy of hypertensive patients which has not yet been sufficiently explored. The data are described in Jacobson's monograph entitled "Progressive Relaxation".[54] Patients find his volume entitled, "You Must Relax",[55] written for the laity, very helpful in attaining the objectives.

Some of the problems which arise may be illustrated by a case report: Mrs. A., a tall blonde woman, sixty years of age, has suffered hypertension for fifteen years. Blood pressure levels have ranged from 160/100 to 240/120. She has suffered eyeground changes, and experienced vascular crises. She is a dynamic person, whom husband and children have relied upon and looked upon as having unlimited endurance. She seems incapable of making certain decisions and the family are unable to do this for her because they are too close at hand; consequently, the patient requires an outsider to help her make up her mind and bear part of the burden of the decisions. This patient owns property which she thinks no one but she can manage. The husband's business office was in the house and it was apparent that the home-office relationship was a very disturbing factor in attaining any degree of relaxation for the patient. It was only after some while, that I succeeded in persuading the family to live in an apartment. There were conflicts because they had always lived in a house and the idea of living in an apartment did not appeal to them. The patient had to remain in her own room day after day because she was unequal to walking the stairs to the living quarter of the house. Once the decision had been made and the objective gained, the wisdom of the change was apparent. It requires constant foresight on my part to see that she does not undertake too much. She has not such a lowered reserve but that she can endure moderate activity, but her idea of a quiet day does not coincide with mine. My efforts are directed at persuading her to engage in relaxing activities rather than the worries of the household which give her concern and result in tension. I have succeeded thus far in having her take an attitude of nonchalance about things. I encourage the attitude that if she can do something about a situation, to do it; but if she cannot, let it go and not worry. But it is an attitude that needs continual encouragement to maintain. When things go wrong, there are the usual symptoms; when life is serene, she is comfortable. The level of blood pressure under these circumstances

may or may not follow the course of the symptoms. It is apparent that these patients are very susceptible to suggestions and encouragement and a well guarded word about level of blood pressure, if they happen to know about it, or an explanation for its change is helpful. Often, if you can remove the cause for the worries, the symptoms disappear. We must be careful, however, not to put too much stress on suggestion, implying a passive rôle on the part of the patients, but rather to encourage an active rôle of their own, such as is involved in the technique of "Progressive Relaxation". Striving to accomplish a task of which they are not capable and uncongenial surroundings, all contribute to the tension state. With careful guidance these may often be rationalized and altered. I have discussed this approach in every day words which may appear to be conceived or expressed vaguely. I am of the opinion, however, that we know too little about this approach, in the scheme of hypertensive therapy, to cloud it with high sounding words which would only cloak our lack of knowledge. Perhaps out of simple beginnings further progress may take place.

There has been very little conscious attention, as I have said, given to this side of therapy, although most physicians in their sympathetic attitude attain the same end. It is an admittedly laborious procedure, but one we must try, if it gives promise of benefit. Because it is time consuming, one clinic in Boston has attempted this form of treatment on a mass basis, by a class method.[56] They have recognized the susceptibility of these patients to suggestion and are turning it to good account. In this class, the nature of hypertension is first explained in simple terms; the rôle apprehension and worry play in it and in symptomology are discussed. In each class period the patients are taught relaxation, and practice it for a short time; and finally recognizing suggestion further, the testimony of a member is heard. Marked improvement in symptoms and in the outlook of the patients is reported to result from this form of therapy and two thirds of them have shown a fall in blood pressure.

In closing may I again say that neither the course of the disease nor its progression may be altered by these techniques, but if we make the subjects more comfortable and happier individuals, it has been worthwhile. I am afraid I have taken liberties with the title, but trust that I have given a perspective of hypertension. I trust also that I have encouraged the point of view of looking upon and of treating the individual as a whole, with attention directed to the "tension" side and to the

psychiatric approach; for symptomatic relief can be given to hypertensives by understanding them and treating them as individuals rather than as just "cases" of hypertension to be treated by drugs which prove of little benefit.

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LIBRARY NOTES

BOOK REVIEW

*Internships and Residencies**

This volume, which consists of an analysis of interns and residencies of 329 pages and an appendix of 148 pages (of which 15 pages are bibliography) is a tremendous piece of work.

It is almost impossible for a reviewer to give a satisfactory account of its contents, as the text is all meat and very few extra words are used. It is a study garnered from interns, attendings, ex-interns, residents and practicing physicians.

The first part of the volume under consideration is taken up by the study of the resources for intern and graduate education in New York, defining teaching hospitals, affiliated hospitals and non-teaching hospitals and defining also the terms of internship, residencies and Fellowships.

This is followed by the history and evolution of the intern and residents.

A most interesting chapter relates to a survey of a questionnaire answered by 1904 practicing physicians, graduates of New York City medical colleges who have had internships in New York. In the introduction there is a very terse statement which really expresses the purpose of this volume. It is as follows: "There has been too much interest in what the interns could do for the hospital and too little consideration to what the hospital could do for the intern."

"Advanced training, as special internships, residencies and Fellowships, have been in the experimental stage, without uniformity of plan or purpose, and the intern groups have suffered from lack of guidance, and clearly defined objectives, and have frequently made poor use of their opportunities."

"The student period from the beginning of the pre-medical course to the end of the internship has averaged from eight to ten years. For their professional careers the demand was long and of arduous proportion, and one might expect an almost uniformly adequate medical qualification." If one follows the recommendations in this volume and the present trends in medical education this average will be increased to at least thirteen years, for the recommendation of the various combined boards demands a two-year rotating internship, followed by residencies of two to five years. This means that the prospective medical student is dependent on his family until he is thirty years of age, a tremendous economic responsibility. To show the scope of this work questionnaires accompanied by personal letters were sent out in 1935 and 1936 from the deans' offices of Columbia, Cornell, Long Island, New York Medical and Flower Hospital, and New York University Medical Colleges, to 3,299 of their graduates for the years 1919 to 1921, 1924 to 1926, and 1929 to 1931. These periods were selected as giving a representative sample of graduates during the fifteen years preceding the time of the present survey. In all, the surprising number of 1904 carefully-answered questionnaires were returned for analysis. The analysis indicates where the men were practicing, the type of work they were doing, and their opinions of the advantages and disadvantages of intern training.

It was found that 20 per cent of the graduates secured appointments on the staffs of teaching hospitals and 26 per cent on the staffs of hospitals with medical school affiliations. Only 12 per cent had no hospital contacts and were therefore completely divorced from

* Report by The New York Committee on the Study of Hospital Internships and Residencies. Jean Alonzo Curran. M.D., Executive Secretary. New York, The Commonwealth Fund; London, Humphrey Milford, Oxford University Press, 1938.

the educational advantages of hospitals.

The volume is replete with numerous tables of analysis of the studies, grouping the surgical and medical specialties separately.

Chapter V, which is full of most valuable material, is concerned with factors contributing to house staff efficiency. This subject is taken up from the point first of physical well-being and efficiency of interns, including health care, housing, call systems, recreation, food, remuneration and uniforms. It is interesting to note that despite the risks taken by the intern on the ambulance and in the hospital he has been protected by insurance only in the rarest instances. Provisions of the State Compensation Law are inadequate when applied to interns, since interns are apprentices and not salaried employees. At the time of this survey only eight of the sixty hospitals studied were making a routine health examination of their interns. The importance of reexamination every six months the committee feels cannot be over-emphasized. The living quarters provided for interns and residents have been inadequate, according to this report, in over half the hospitals of New York City.

There is an excellent chapter on hospital libraries and the use of these libraries. It has been found that the interns are stimulated to reading largely by the attending staff and also it has been found that a resident librarian is necessary in order to have the library properly protected.

A very interesting and important subject considered is the introduction of the intern to the hospital. The first hours of an intern after his entrance into a hospital may influence his entire hospital career. If the seniors on the staff have a pessimistic attitude toward the hospital and toward the attending staff his reaction is apt to be influenced. In the reviewer's experience it took three years to change the morale of a hospital staff so that it became loyal supporters of a new regime. The committee believes that a member of the attending staff should be assigned for the instruction of each intern entering the hospital. Where this is impossible manuals and procedure books presented to each intern on admission have proven satisfactory. A voluminous manual, however, has frequently prevented the intern from mastering its contents. The committee recommends a hand-book containing merely the outline of the hospital's methods in current use. This book must be revised every few years in order to prevent its becoming obsolete. The following subjects are considered necessary for such a manual:

1. Organization of the house staff, with an outline prescribing the duties of each member.
2. The relationship of the intern to the hospital administration, attending, nursing, social service, and technical staffs.
3. Attitude toward patients.
4. Outline for record of the history, physical examination, progress notes, and case summaries.
5. Special diagnostic and therapeutic technics.
6. The handling of emergencies.
7. Laboratory procedures.
8. Nursing technics.
9. Social service utilization.
10. Diets.
11. Operating and delivery room methods.
12. Methods of securing consent to necropsy.

The committee states: "With or without an intern 'bible' there has been no satisfactory substitute for painstaking teaching and supervision of each new staff member."

Chapter VIII is largely concerned with the most important subject of the entire volume —the dividing of hospital services. In this a thorough study of the rotating or straight service is analyzed, and the committee recommends that the fundamentals of an internship preparing for general practice should consist of rotation through medicine, surgery, gynecology and obstetrics, and pediatrics. It was felt that during a two-year experience the time allowance for each of these services should not be less than the following:

Medicine — six months
Surgery — six months
Gynecology and obstetrics — three months
Pediatrics — three months

They conclude that the quality of service and

incidentally the educational benefit to the intern are in most instances directly proportionate to the time spent on the service. This applies to the mixed and straight, as well as rotating internships. While the duration of each block of assignment is only one factor in producing a high grade of internship, it is manifestly an essential ingredient in a successful formula.

In studying the case load and the size of the intern staff the committee states that in general the hospitals with services of acute conditions show the best quality of medical attention and intern teaching when they had census loads of ten to fifteen patients per house staff member. It was observed further that ratios above fifteen acute cases per man were prejudicial to quality of medical service and intern instruction. This was specially evident in the hospital where the ratio rose to twenty to thirty per intern.

In an analysis of internships it was found that the greatest shortcomings in teaching were, first, the instruction in such diagnostic and therapeutic methods as venipuncture, paracentesis, spinal tap and examination of body orifices. In less than one-third of the hospitals has such instruction been systematically provided. The average intern completing his service seems to be incompetent in examination of the ear, nose and throat, pelvis, anus and rectum. The second fundamental deficiency is the time allotted to the out-patient department. It is well known that the majority of cases appearing in the office of the young practitioner are the types of cases seen in the out-patient department.

The chapter on residencies and fellowships is splendidly presented, but space will not allow an adequate description of this chapter. It is discussed under the following subtitles: Duties and opportunities of the resident, advantages to the hospital of a resident staff, distribution of residencies by specialty, length and plan of the residencies, evaluation of residencies as adequate training, attitude of staff members and others toward residencies and the opinion of interns. The committee believes that there should be an internship of at least two years before the beginning of a residency in any of the specialties, and the conviction of the committee is that a residency experience of less than two years is an inefficient arrangement both for the hospital and as a training experience. The committee strongly recommends in this study the necessity of out-patient department experience. A summary of the various types of residencies in the medical and surgical specialties is adequately discussed, with the demands of the various American boards of specialties. In summarizing the residencies in the different types of hospitals and services the committee states that it has been found that residencies elevate the quality of medical service in the hospital and improve the teaching given the interns and medical students: Moreover the residencies provide an excellent opportunity for original investigation, for correlating the training in the basic sciences and for grounding in the essentials which must be included in the specifications of a specialist.

In concluding an analysis of this volume the average practitioner who is head of a hospital service is impressed with the idealization presented by the committee and the necessity for revising his own hospital service. Unfortunately, if he should live up to all of the requirements of this volume he would have to limit his private practice in order to put almost full time on teaching of interns and residents.

I should advise every chief of a hospital service to read this volume.

F.W.B.

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IN MEMORIAM

Edwin Beer

1876 - 1938

When Edwin Beer died on August 13, 1938, at the age of 62 years, the medical profession lost a man of integrity and distinction, a trusted leader, a clear thinker, loyal to his professional obligations, to family and to friends.

He was born in New York City, where he was graduated B.A. from Columbia College in 1896, and received, in 1899, his medical diploma form the College of Physicians and Surgeons. After serving his internship at the Mount Sinai Hospital he studied abroad, at Berlin, Vienna and Prague and, on his return, resumed his association with the Mount Sinai Hospital and was also connected with the staffs of the Lenox Hill and the Flower Hospitals. He established the cystoscopic clinic at Lenox Hill and thus early attested his interest in what was to be his chosen specialty. His association with the Mount Sinai continued until his death. He was attending surgeon from 1910 and served as president of the board with distinction.

The soundness and the breadth of his interest in fundamental medical problems as well as those of the practitioner is attested by the scope of his medical writings and by the basic sanity that characterized them. His first papers, published in 1904, five years after graduation, were entitled "Adrenal Rests in the Liver" and "Diverticula of the Intestine". Thereafter for a number of years he was inclined toward neurological surgery and was attached to the Neurological Institute but, in 1910, when he assumed charge of a service at Mount Sinai he definitely asserted his interest in urology and in this same year he achieved the physical treatment of bladder tumors with the Oudin high frequency current, introducing, for the first time, a practical therapy for the most frequent type of bladder neoplasm, the papillary tumor. This therapy has revolutionized the treatment of bladder tumors. His monograph on Tumors of the Urinary Bladder was published in 1935. This great work was recognized first by the International Society of Urology through the initial award of its Gold Medal for service to urology to Dr. Beer, in 1927, and again by the award from the American Congress of Physical Therapy, of its Gold Key, in 1937.

His other outstanding contribution to urology was the perfection of the first practical cystoscope for children, experience with which authorized the publication, in 1930, of his monograph on "Diseases of the Urinary Tract in Children", the first extensive investigation of this subject to appear in print.

He was, at various times, president of the Medical Board of Mount Sinai Hospital, president of the New York Surgical Society and vice-president of the Academy of Medicine. He served during what we have not yet learned to cease calling the World War as Lieutenant Colonel in the Medical Corps,

U. S. Army. In the last year of his life his friends at the Mount Sinai Hospital instigated and surgeons, pathologists and urologists from the world over contributed to a *Festschrift* in his honor.

This was a man as straight and true in his professional as in his personal relations, the good physician. Throughout his life his profound interest was in his profession. The constant application of his clear mind developed in him both judgment and wisdom. He put up with no shams and thus gathered around him a group of devoted followers and students. To his hospital, to the Academy while an officer, and to his students and assistants, in particular, he was always the patient, loyal friend and lucid teacher.

Honesty, a devoted diligence, surgical skill, a fearless and a lucid and inquiring mind; these were his attributes. He will indeed be missed.

EDWARD L. KEYES

FREDERICK TILNEY

1876 - 1938

With the death of Dr. Frederick Tilney on August 7, 1938 there passed one of the leaders of American medicine who did much to shape the form of Neurology not only in New York City but in the Nation. Dr. Tilney's career was a typical American one in that all that he received of honors and affection he earned by his hard work and his rigid scientific honesty.

Dr. Tilney was born into a cultured family in Brooklyn on June 4, 1876. After being graduated from the Brooklyn Polytechnic Institute in 1892 he entered Yale University where he was graduated in 1897 with the degree of A.B. At first he tried newspaper work on the old "New York Sun" but soon he decided that medicine was to be his field. At the Long Island College of Medicine he worked and played with an exceptional group of classmates, many of whom later also made their mark in the medical world. These friendships, which lasted till his death, surely helped to form that medical mind that later was to be the greatest leader of them all. After his graduation from the Long Island College of Medicine in 1903 he served an internship in the Kings County Hospital and then started his practice of medicine in Brooklyn.

From the start his interests were in research as well as practice and never in his life did he get too busy with practice to neglect his research work.

In 1906, with a problem of the hypophysis on his mind, he applied to Dr. T. Mitchell Pruden at the College of Physicians and Surgeons for facilities to work. Thus began an affiliation with P. & S. which was to last for over thirty years. After a year in Dr. Pruden's laboratory he transferred his activities to the Anatomical Laboratory of Dr. George S. Huntington. Here Tilney first really found himself. Dr. Huntington was a scientist of his own stamp, fearlessly honest, hard working and as sceptical of himself as he was unsparing of his time and energies. A deep and lasting friendship grew steadily between these two men who were alike in so many ways. Probably New York has seldom seen a personal and scientific friendship that was as intense and as lasting as that one. Only those who worked with Dr. Huntington know just what that means.

Under Dr. Huntington's stimulus Dr. Tilney naturally followed the path of his greatest interest in life—the nervous system. He had written on the nervous system before and he only followed his own bent. First as instructor of anatomy he taught embryology, cranial morphology and neuro-anatomy both at Columbia and at his medical Alma Mater. In 1914 he was appointed Associate Professor of Neurology at the College of Physicians and Surgeons and in 1915 was made Professor of Neurology and head of the department and there he remained until his death.

The history of Tilney's development of the Department of Neurology in P. & S. is an interesting story. It was a small department when he took it over and under his hand it became a major one. Neuro-anatomy and neuropathology were joined with clinical neurology to form this new department. While formerly only clinical neurology was taught and that only to third and fourth year students, gradually the others fell into line until finally the department was teaching neurology from the ground up in all the four years of the medical course. The Neuro-

logical clinic at the Vanderbilt Clinic was built up at the same time and by the same methods of careful, conscientious, honest work. For a number of years he worked in the clinic every afternoon seeing patients, directing treatments, and teaching. This devotion to his department rapidly drew to him the kind of assistants he liked to have. The department has always been his department.

In 1919 Dr. Tilney was appointed to a service in The Neurological Institute of New York. Ten years later the Neurological Institute merged with the Department of Neurology at Columbia University and the two moved up-town together to the new Neurological Institute building in the Columbia-Presbyterian Hospital Medical Center. The credit for that move is largely Dr. Tilney's.

The fall of 1924 saw his first and only set-back. He was stricken with right hemiplegia and aphasia. Such a blow would have finished the career of a lesser man. His come-back from that catastrophe was a source of enthusiastic inspiration to all his friends. Never did he think himself defeated but always he fought his way back. First he got back his speech and with it his old command of beautiful English and his oratory. He learned to walk again with hardly a limp and he learned to write with his left hand. He learned to get help from others in purely mechanical procedures and his research work and practice went on at a tempo not diminished. Four years after his illness he published his monumental work "The Brain from Ape to Man" which has taken a high place among the scientific publications of neurology and comparative anatomy.

After Dr. Tilney moved from Brooklyn to New York in 1917 his influence grew. His large busy private practice made great inroads into his time but never so much as to wean him away from his first love, neuroanatomical research. Tilney was of the type of the old fashioned research man. Dr. Huntington was ever his model. Tilney, like his preceptor, knew tissue intimately. He knew from personal experience the preparation and staining of brain sections. In his early years he did it all himself but later, when time was pressing, he had to have technicians to do this work for him—technicians whom he trained and taught the work that he knew so well. At his death he was still working on the hypophysis.

Recognition came early to Dr. Tilney and came to him all the rest of his life. He was secretary and treasurer of the Brooklyn Neurological Society 1907 and 1908 and president 1911 and 1912; President of the New York Neurological Society 1917; Secretary-Treasurer of the American Neurological Association 1917-1925 and president 1926; one of the founders of the Association for Research in Nervous and Mental Diseases and of the New York Society for Clinical Psychiatry. When the Archives of Neurology and Psychiatry was established in 1919 he became one of the editors and retained that post till 1934. He founded the Bulletin of the Neurological Institute and always directed its editorial policies. His interest in the New York Academy was always one of his first. He was vice-president of the Academy from December 1931 to December 1933. In 1935 he was elected a trustee and served until his death. Besides the societies mentioned he was also a member of the American Psychiatric Association, The New York Psychiatric Society, The Galton Society, The Association of American Anatomists, The Philadelphia Neurological Society, The Royal Society of Medicine, London and the Society of Psychiatry and Neurology of Vienna. Besides these he served as Medical Director of the New York Neurological Institute 1935 to 1938 through a trying period of its career. In 1912 Columbia University awarded him the degree of Ph.D. and in 1929 the honorary degree of Sc.D.

Dr. Tilney's influence was great and probably its most lasting effects are seen in the stimulus he gave to younger people to work in scientific medicine. All who worked with him felt the impetus of his enthusiasm and the reward of his approval. His friends remember him for many things and one of those which no one could forget was his laughter. With a fine sense of humor he loved a joke and a good story. He enjoyed laughter and when he laughed he did so, as he did everything else, with his whole being. Every fiber of his big robust frame seemed to enter into his laughter and he gave himself completely to the enjoyment of it. Probably only

a man who could laugh like that could have risen above hemiplegia and, after it had tried to strike him down, have done the best and most enduring work of his career.

The stimulus of his energy and his personality; the honesty of his research work and his reporting of it; the sincerity of his devotion to neurology and his teaching; the charm of his culture and his friendship blended to form the Fred Tilney his friends loved. All these we shall miss over the years that are to come.

LOUIS CASAMAJOR

DEATHS OF FELLOWS

BEER, EDWIN: 45 East 85 Street, New York City; born in New York City, March 28, 1876; died in New York City, August 13, 1938; received the degree of Bachelor of Arts from Columbia University in 1896 and graduated in medicine from the College of Physicians and Surgeons, Columbia University in 1899; elected a Fellow of the Academy December 7, 1905.

Dr. Beer was elected a Vice-President of the Academy December 1928 and served until December 1931.

Dr. Beer, who was a former Chairman of the Medical Board of the Mount Sinai Hospital, was attending surgeon to this institution. He was consulting surgeon to the Bellevue Hospital.

In 1927 Dr. Beer received the first gold medal of the International Society of Urology at Brussels. The honor was for his "original work on the application of high frequency current for the curing of intravesicular diseases." He held certificates from the American Board of Urology and the American Board of Surgery.

Dr. Beer was a member of the American Urological Association, the American Surgical Association, the New York Pathological Society, the New York Surgical Society and one of its former presidents, the Clinical Society of Genito-Urinary Surgeons and the County and State Medical Societies. He was a Fellow of the American College of Surgeons and the American Medical Association.

FRASER, ALEXANTER: 153 West 11 Street, New York City; born in Nova Scotia, 1869; died in Beechurst, Long Island, New York September 18, 1938; graduated in medicine from Dalhousie University Medical College, Halifax, Nova Scotia, in 1897; elected a Fellow of the Academy April 1, 1920.

Dr. Fraser who was a former professor of pathology at New York University and Bellevue Medical College, was pathologist to the St. Vincent's Hospital and consulting pathologist to the New York Foundling, People's, Polyclinic and Mammouth Memorial Hospitals. He was a Fellow of the American Medical Association and a member of the Harvey Society, the New York Pathological Society and the County and State Medical Societies.

SENIOR, HAROLD DICKINSON: Salsbury Cove, Maine; born in Croydon, England, October 30, 1870; died in New York City, August 6, 1938; graduated in medicine from the Royal College of Physicians and Surgeons in 1892; received the degree of Bachelor of Medicine from Durham University in 1895 and Doctor of Science from Syracuse University in 1910; elected a Fellow of the Academy April 20, 1911.

Dr. Senior was house surgeon and physician to the Charing Cross Hospital, London, 1892-93; assistant demonstrator of anatomy at the Charing Cross Hospital Medical School, 1894-95; demonstrator of anatomy at the Medico-Chirugical College in Philadelphia, 1902-04; associate in anatomy at the Wistar Institute of Anatomy and Biology, 1904-07; professor of anatomy at Syracuse University 1907-10; and professor of anatomy at New York University, 1910-36 when he was designated professor emeritus of that institution.

Dr. Senior received from Durham University in 1918 the award of an honorary degree and designation as the institution's gold medalist for the year. For many years Dr. Senior was an associate editor of the American Journal of Anatomy.

He was a Fellow of the American Association for the Advancement of Science and a member of the Anatomical Society of Great Britain and Ireland.

SCHWEINITZ, GEORGE EDMUND de: 1705 Walnut Street, Philadelphia, Pennsylvania, born in Philadelphia, October 26, 1858; died August 22, 1938; graduated in medicine from the University of Pennsylvania in 1881; elected an Honorary Fellow of the Academy, November 18, 1926.

Dr. de Schweinitz was professor of ophthalmology at Philadelphia Polyclinic 1891 to 1894, and at Jefferson Medical College 1892 to 1902. He taught at the medical school, Pennsylvania University, from 1902 to 1924, and at the Graduate School of Medicine from 1924 to 1928. He was a vice-president of the Pennsylvania Institute for Instruction of the Blind, a trustee of the University of Pennsylvania, a Fellow of the American Medical Association and its President, 1922-1923, a Fellow of the American College of Surgeons, a member of the American Ophthalmological Society and its President in 1916, a member of the American Academy of Ophthalmology and Otolaryngology and a member of the Philadelphia Medical, Neurological and Pathological Societies. He also was a member of the American Philosophical Society, the Ophthalmological Society of the United Kingdom, the Société Francaise d'Ophtalmologie and the Société Belge d'Ophtalmologie.

When the United States entered the World War, Dr. de Schweinitz received a commission in the Army Medical Corps and served in the American Expeditionary Force in France as consultant in ophthalmology, reaching the rank of Colonel prior to the Armistice and subsequently, Brigadier General in the Reserve Corps. He was member of the Editorial Board of the Medical and Surgical History of the World War. Dr. de Schweinitz wrote many books and articles on ophthalmological and neurological subjects.

The degree of Doctor of Science was awarded him by the University of Michigan in 1922 and Harvard University in 1927. He held a certificate from the American Board of Ophthalmology.

Dr. de Schweinitz was the recipient of the Howe prize medal in ophthalmology in 1927, the Hugenot Cross in 1928, and the Leslie Dana medal for work in the prevention of blindness in 1930.

TILNEY, FREDERICK: 920 Fifth Avenue, New York City; born in Brooklyn, New York, June 4, 1876; died in New York City, August 7, 1938; received the degree of Bachelor of Arts from Yale University, New Haven, Connecticut, in 1897; graduated in medicine from the Long Island College Hospital in 1903; received from Columbia University the degree of Doctor of Philosophy in 1912 and the honorary degree of Doctor of Science in 1929; elected a Fellow of the Academy October 7, 1915.

Dr. Tilney served the Academy as a Vice-President from January 1932 to January 1934, and as a Trustee from January 1936 until his death.

Since 1935 Dr. Tilney has been Medical Director of the Neurological Institute, after having been for several years chairman of the Institute's Committee on Medical Research. He was also professor of neurology and neuro-anatomy at Columbia University, College of Physicians and Surgeons, and consulting neurologist to the Presbyterian, Roosevelt, Brooklyn, Methodist Episcopal, Babies and Greenwich Hospitals.

Dr. Tilney was a Fellow of the American Medical Association and a member of the American Neurological Association, the American Psychiatric Association, the Association for Research in Nervous and Mental Disease, the American Association of Anatomists and the State and County Medical Societies.

TOREK, FRANZ JOHN ALBERT: 108 East 82 Street, New York City; born in Breslau, Germany, April 14, 1861; died in Vienna, September 19, 1938; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1887; elected a Fellow of the Academy January 15, 1891.

Dr. Torek was consulting surgeon to the Lenox Hill and Post-Graduate Hospitals. He was a Fellow of the American College of Surgeons and the American Medical Asso-

ciation, a member of the American Association for Thoracic Surgery and a former president, the American Surgical Association, and the County and State Medical Societies.

WHEELER, JOHN MARTIN: 635 West 165 Street, New York City; born in Burlington, Vermont, November 10, 1879; died in Underhill Center, Vermont, August 22, 1938; received from the University of Vermont the degree of Bachelor of Arts in 1902; Doctor of Medicine in 1905; Master of Science in 1906; and the honorary degree of Doctor of Science in 1928. He also received the honorary degree of Doctor of Science from the Middlebury College in 1933.

Since 1928 Dr. Wheeler was professor of ophthalmology at Columbia University and director of the Eye Institute of the Presbyterian Hospital. He was consulting ophthalmologist to the Reconstruction and a unit of the Post-Graduate Hospitals. He was consulting ophthalmological surgeon to Bellevue, Sloane, Neurological Institute, Psychiatric Institute, Babies, Hackensack Hospital of New Jersey and St. Luke's of Newburgh.

Dr. Wheeler held a certificate from the American Board of Ophthalmology and was a Fellow of the American College of Surgeons and the American Medical Association, and was a member of the American Ophthalmological Society, the American Academy of Ophthalmology and Otolaryngology and the State and County Medical Societies.

Dr. Wheeler received the Leslie Dana gold medal in 1936, awarded by the National Society for the Prevention of Blindness for his "outstanding achievement in the prevention of blindness and the conservation of vision."

He contributed many articles on diseases of the eye.

ANNOUNCEMENTS

When in 1928 the Academy was fully established in its new home and had at its disposal additional space and funds in connection therewith, the Council authorized the President to appoint a special committee to consider expansions of Academy activities thus made possible. This committee submitted a comprehensive report which received the approval of the Council in April 1929, at which time the report was published and made available to the membership. The administration, during the intervening nine years, has endeavored to carry out the broader policies adopted by the Council. As a result, the Academy has become an institution of great influence, to which many agencies in the fields of medical education, public health and social welfare appeal.

Inasmuch as these policies not only involve considerable expenditure of time and of money, but also because a gradual extension of the field of interest of the Academy has occurred, it now seems advisable that all of the activities of the Academy be again reviewed and carefully reconsidered in order to determine the relative value of each and its place both in the programme and in the financial budget of the Academy.

Toward this end a second Committee on Activities has been appointed by the Council and is now at work upon the subject.

It is important that as far as possible the officers of the Academy know the views of the Academy membership as individuals. For this purpose the Council cordially invites the Fellows and Members of the Academy who so desire to express an opinion upon the general principles involved and the details of the programme.

Communications may be addressed to Dr. George Baehr, Chairman of the General Committee, or to any of the following Chairmen of the Reference Committees at the Academy building, care of the Director's office:

Dr. Samuel A. Brown, Chairman Reference Committee on Administration

Dr. Arthur F. Chace, Chairman Reference Committee on Sections and Scientific Meetings

Dr. Rufus I. Cole, Chairman Reference Committee on Library

Dr. Herbert B. Wilcox, Chairman Reference Committee on Medical Education

Dr. DeWitt Stetten, Chairman Reference Committee on Public Health Relations

Dr. I. Ogden Woodruff, Chairman Reference Committee on Medical Information Bureau

Dr. Frederic Sondern, Chairman Reference Committee on Miscellaneous Items

Signed for the Committee

JAMES ALEXANDER MILLER,
President

LEWIS FRISSELL,
Secretary

CHANGE IN SUBSCRIPTION RATE

Subscribers to the Bulletin of The New York Academy of Medicine are advised that the Council of the Academy has authorized a change in the subscription price for this Journal, from two to three dollars a year, effective January 1, 1939.

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